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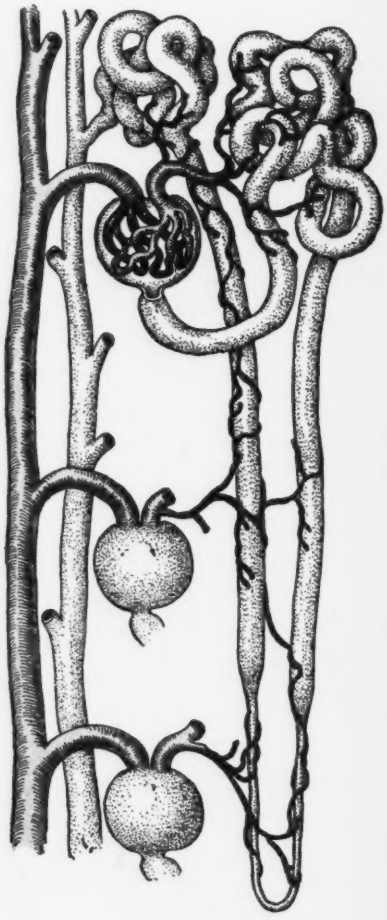

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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

# Cardiocirculatory Performance in Atrial Flutter

By RÉJANE M. HARVEY, M.D., M. IRENÉ FERRER, M.D., DICKINSON W. RICHARDS, M.D. AND ANDRÉ COURNAND, M.D.

Data obtained in 12 patients with atrial flutter indicate that this arrhythmia was associated with a low cardiac output in those subjects with intrinsic heart disease. Furthermore, the resting level of blood flow increased somewhat when the cardiac mechanism of five patients with atrial flutter was converted to sinus rhythm. In two cardiac patients, the response to exercise in flutter as compared to normal sinus rhythm was little different. Lesser circulation pressures in the absence of heart failure were not abnormal in atrial flutter but, in general, when failure existed, the type of pulmonary hypertension noted in subjects with flutter, differed from those in sinus rhythm. Tricuspid insufficiency did not occur in atrial flutter in contrast to its almost constant appearance in atrial fibrillation. Atrial systolic pressure waves, associated with each electric flutter wave, were ubiquitously present in all lesser circulation pressure curves. Their origin is discussed.

ALTHOUGH the electrocardiographic nature of atrial flutter has been extensively studied for many years and certain electrophysiologic aspects of this arrhythmia are still under discussion,[1, 2] its hemodynamic effects in man have been relatively unexplored except for the observations of Ritchie[3, 4] and Lewis[5] regarding venous pulse waves. The present report is concerned with an evaluation of cardiocirculatory performance in patients with this arrhythmia as defined by some of the modern physiologic methods.

As a result of such studies carried out in 12 subjects with atrial flutter, using the cardiac catheterization technic, certain facts have become apparent regarding circulatory performance in this arrhythmia. The basic pressure patterns observed within the right heart cavities have proved to be of some interest and will be discussed in detail. Furthermore, the influence of atrial flutter upon blood flow and blood pressures was sought in studies made at rest, during exercise, in the presence of congestive heart failure, and after conversion to sinus rhythm.

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## Material and Methods

Of the 12 patients comprising this report 11 had heart disease of the following etiologies: seven arteriosclerotic, one hypertensive, one hypertensive and arteriosclerotic, one rheumatic and one constrictive pericarditis. The twelfth patient had no evidence of heart disease. In all 12 right heart and brachial artery pressures were recorded, using either the manometric system of Hamilton or strain gage pressure transducers and a photo-oscillographic technic.* The methods utilized to measure blood pressures, cardiac output (using the Fick principle), and blood

The work described in this paper was supported by a grant from the Life Insurance Medical Research Fund, and by a research grant (PHS Grant H-833 (C)) from the National Heart Institute of the National Institutes of Health, Public Health Service.

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* Using a pressure recording machine manufactured by Electronics for Medicine, Inc., New York, N. Y.

TABLE 1.—*Hemodynamic Data in Nine Patients With Atrial Flutter*

| Case, Sex Age, BSA | Diagnosis | AR:VR (beats/min.) | Card. Index (L./min./M.² BSA) | Stroke Volume (cc.) | $O_2$ Consump. (cc./min./M.² BSA) | R.Q. | AV diff. (vol. %) | Arterial blood $O_2$ | | Pressures in mm. Hg | | | TBV (cc./M.² BSA) | PV (cc./M.² BSA) | H'crit. (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Cont. (vol. %) | Sat. (%) | Brachial art. s/d, m | Pulmon. art. s/d, m | Rt. vent. d | | | |
| Normal | | 70:70 | 3.12 | 70 | 131 | 0.80 | 4.2 | | 96 | 120/70, 90 | <30/10, 15 | <5 | 2750 | 1500 | 45 |
| (a) No Heart Disease | | | | | | | | | | | | | | | |
| #457. M. 58 years. 1.98 | Paroxysmal Atr. Flutter | 340:85 | 2.57 | 60 | 144 | 0.75 | 5.6 | 18.7 | 96 | 123/75, 96 | 22/13, 16 | 4 | 2525 | 1380 | 46 |
| (b) Heart Disease Without Congestive Failure | | | | | | | | | | | | | | | |
| #684. M. 68 yrs. 1.86 | ASHD. | 300:87 | 2.00 | 43 | 148 | 0.74 | 7.4 | 19.7 | 98 | 126/77, 106 | 20/6, 11 | 4 | 2730 | 1369 | 50 |
| #777. M. 65 yrs. 1.78 | H & ASHD. EH. | 340:68 | 2.10 | 55 | 126 | 0.90 | 6.0 | 17.6 | 96 | 187/97, 128 | 26/14, 19 | 4 | 2572 | 1545 | 42 |
| #324. M. 53 years. 1.55 | ASHD. EH. | 320:160 | 1.67 | 16 | 122 | 0.89 | 7.3 | 14.0 | 81 | 102/74, 82 | 26/—, — | 0 | 3460 | 1840 | 47 |
| (c) Heart Disease With Congestive Failure | | | | | | | | | | | | | | | |
| #405. M. 65 yrs. 2.10 | ASHD. EH. | 300:150 | 2.48 | 35 | 147 | 0.79 | 5.9 | 13.5 | 87 | 109/72, 84 | —, — | 10* | 4140 | 2470 | 40 |
| #542. M. 49 yrs. 1.65 | ASHD. EH. | 250:135 | 1.58 | 19 | 142 | 0.75 | 9.0 | 16.0 | 97 | 116/93, 102 | 52/36, 45 | 15 | 3660 | 2000 | 45 |
| #477. M. 56 yrs. 1.81 | ASHD. EH. RBBB. | 300:200 | 1.85 | 17 | 122 | 0.89 | 6.6 | 18.9 | 95 | 106/81, 87 | 22/16, 17 | 9 | 3930 | 2110 | 46 |
| #695. F. 44 yrs. 1.73 | RHD. EH. MS. | 230:115 | 1.48 | 22 | 117 | 0.81 | 7.9 | 16.1 | 89 | 128/90, 105 | 32/22, 26 | — | 3150 | 1698 | 46 |
| #619. M. 28 yrs. 1.75 | Chr. Con. Peri. EH. | 250:75 | 1.62 | 38 | 131 | 0.92 | 8.1 | 19.8 | 97 | 116/89, 93 | 32/22, 26 | 20 | 5360 | 2480 | 53 |

ASHD = Arteriosclerotic Heart Disease
H and ASHD = Hypertensive and Arteriosclerotic Heart Disease
EH = Enlarged Heart
RBBB = Right Bundle Branch Block
RHD = Rheumatic Heart Disease
MS = Mitral Stenosis
Chr. Con. Peri. = Chronic Constrictive Pericarditis
TBV = Total Blood Volume
PV = Plasma Volume
H'crit = Hematocrit
* = Read off right atrial curve.

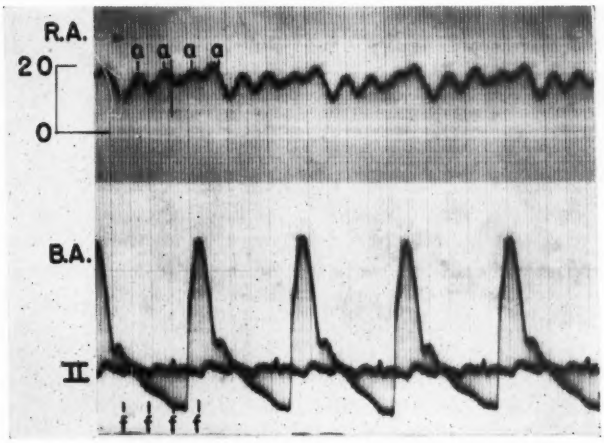


FIG. 1. Pressure curves in atrial flutter. The upper curve is recorded from the right atrium (R.A.), with scale in mm. Hg to the left, and the lower curve is from the brachial artery (B.A.) through which runs standard lead II. The letter *a* indicates atrial systole and the letter *f* the electrical flutter wave. The vertical line drawn through the atrial tracing indicates the onset of ventricular systole. The curves in this figure and figures 3 through 7 were recorded by the use of strain gage pressure transducers and photo-oscillographic technic. All curves have vertical time lines inscribed every 0.04 second.

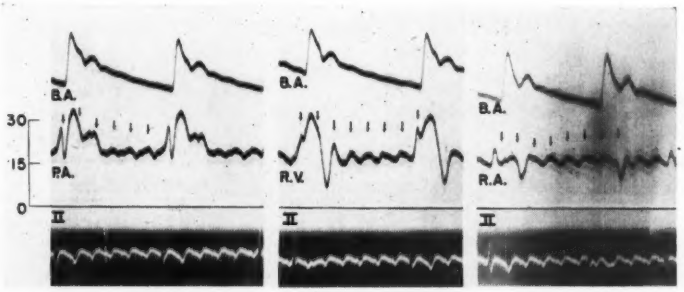


FIG. 2. Pressure curves in a patient with atrial flutter and constrictive pericarditis. The upper curve in all three frames is from the brachial artery (B.A.) beneath which, reading from left to right, are recorded (using Hamilton manometers) the pulmonary artery (P.A.), right ventricle (R.V.) and right atrial (R.A.) tracings. The scale for these tracings lies on the left and is expressed in mm. Hg. Standard lead II appears at the bottom of each frame. The small arrows indicate atrial systoles.

volume at rest, during exercise and following acute digitalization, as well as criteria employed for interpretation of results, have been published previously.[6, 7] Diagnostic details of the nine patients in whom complete hemodynamic measurements were made, appear in table 1.

## DISCUSSION OF RESULTS

*Mechanical Events.* Examination of the pressure curves in atrial flutter has revealed several interesting features. First, inspection of the right atrial curves reveals the presence of a mechanical atrial activity with each electrical flutter wave, as can be seen in figure 1. The rapid regular atrial systolic waves, occurring at a rate of 230 per minute and marked with the letter a, in this patient with a flutter rate of 230 and a 4:1 A-V response, are not unexpected since Sir Thomas Lewis and other workers have suggested their occurrence from waves seen in the jugular pulse contour.[3-5] The height of these systolic waves obviously varies with the state of atrial distention which in turn is influenced by venous return, ventricular systole and the opening of the tricuspid valve.

These atrial systolic waves can also be seen during right ventricular diastole as well, as is apparent in figure 2 which represents tracings taken from a patient with constrictive pericarditis and atrial flutter. These regular atrial pressure waves are identical with those seen in the atrial curve in the same figure. This is a logical expectation since the ventricle and atrium are common chambers at this time of the cardiac cycle. However in this same figure 2 one also notes these regular oscillations on the pulmonary artery tracing during diastole. Inasmuch as the pulmonary artery is obviously not communicating with the right ventricle at this time, the pulmonary valve having closed, one could attribute these oscillations to impacts produced by left atrial systoles and transmitted directly to the adjacent wall of the main pulmonary artery. These oscillations are also present during the ejection phase in both the right ventricle and pulmonary artery tracings (fig. 2), which lends further support to the assumption that they are direct impact phenomena. It is less likely that they are generated by catheter motion as they do not resemble the usual artefacts since their frequency is much lower. Furthermore since these manifestations of atrial activity have also been seen on brachial artery pressure tracings secured by means of an indwelling needle, as recently described by Howarth,[8] the presence of the catheter would appear unimportant in their production. Since these waves occur in the pulmonary artery curves in patients without pulmonary congestion, as evidenced by normal pulmonary artery diastolic pressure, as seen on the left of figure 3, retrograde transmission of these oscillations through the capillary bed from the left atrium, which has been suggested to explain the contour of the pulmonary artery wedge pressures, seems unlikely.

It is interesting to contrast the curves recorded in atrial flutter with those seen in

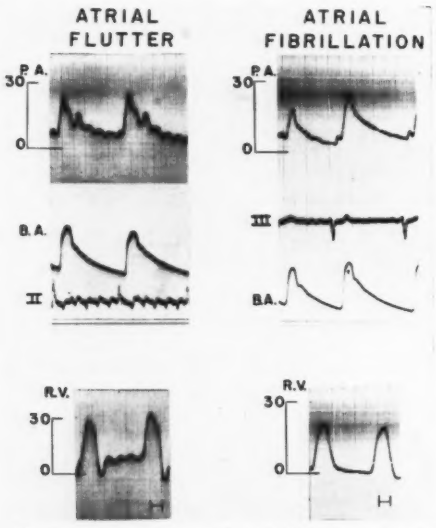


FIG. 3. Pressure curves in atrial flutter and atrial fibrillation. Comparison of pulmonary artery (P.A.) curves above, brachial artery (B.A.) in the middle, and right ventricle (R.V.) below, with the scale in mm. Hg to the left, can be made between flutter in the frame on the left and fibrillation on the right. Note that lesser circuit pressures are normal in both instances. The standard leads II and III are appropriately indicated. The time interval between bars is 0.20 second.

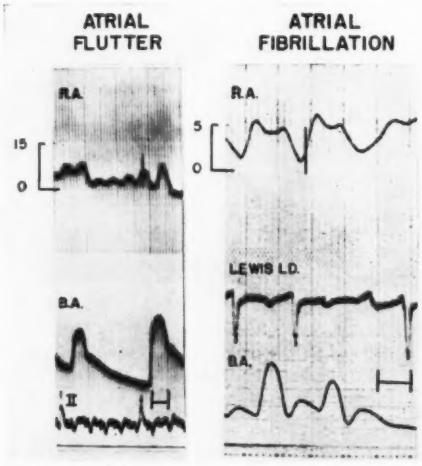


FIG. 4. Atrial pressure curves in atrial flutter and atrial fibrillation. The atrial tracings on the upper line were recorded at different sensitivities as can be seen by referral to the left hand scale (in mm. Hg). The vertical lines through the atrial curves indicate the onset of ventricular systole. The curves of flutter in the left frame were inscribed with standard lead II, while a Lewis lead was used in the fibrillation recording. The paper speed was faster (75 mm. per second) in the right hand frame where the enclosed time interval of 0.20 second at the lower right hand corner can be compared to the same interval in the left hand curves.

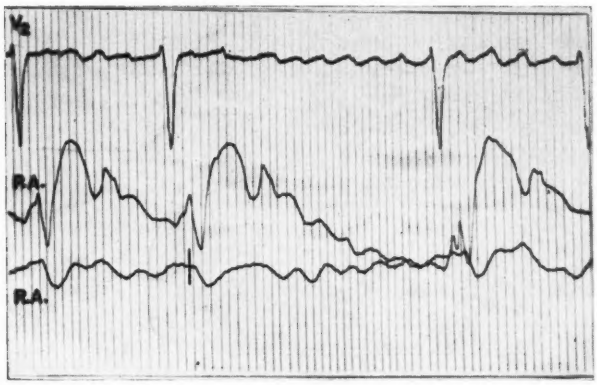


FIG. 5. Simultaneous right atrial (R.A.) and pulmonary artery (P.A.) curves in a patient with flutter-fibrillation. Lead $V_2$ was used and a rapid paper speed of 75 mm. per second. Time lines were inscribed every 0.04 second. The vertical line indicates onset of ventricular systole.

the closely related arrhythmia, atrial fibrillation, since in the latter, individual atrial systoles cannot always be identified in the pulmonary artery or right ventricular curves as is shown in the right frame of figure 3. Furthermore, they are not usually seen on the atrial curves as indicated in the right hand frame of figure 4. This difference in mechanical activity of the atria may be of interest when one considers the nature of these two arrhythmias as recently discussed by Prinzmetal.[1] In atrial fibrillation it is clear that the atrial curves give no pressure evidence of any mechanical activity produced by the atrial electrical stimuli and indeed change their contours only in relation to the ventricular events. It is impossible to learn whether this absence of effective atrial systole is the reflection of disordered electrical stimulation as inferred by Prinzmetal,[1] resulting in a disordered but continuous state of shortening fibrils none of which act in concert to produce a volume change in the chambers; or whether the prime difficulty is the rate of stimulation which in itself, and apart from its irregularity, is too rapid to permit relaxation of any atrial segment, thus producing a state of ineffective tetany.

Some additional information can be secured from examination of the atrial curve obtained in a patient considered to have so-called flutter-fibrillation (figs. 5, 6, and 7). This diagnosis was reached because the electrical atrial complexes were irregular in contour and occurrence and the atrial rate was 428, a value thought to be intermediate between classical atrial flutter and fibrillation. Atrial systolic waves can be seen in the right atrial and pulmonary artery curves (figs. 5 and 7) and the right ventricular and pulmonary artery tracings (fig. 6), recorded simultaneously by means of a double lumen catheter. This suggests that when in the course of fibrillation atrial rates fall into a slower range, which more nearly approximates flutter rates, and

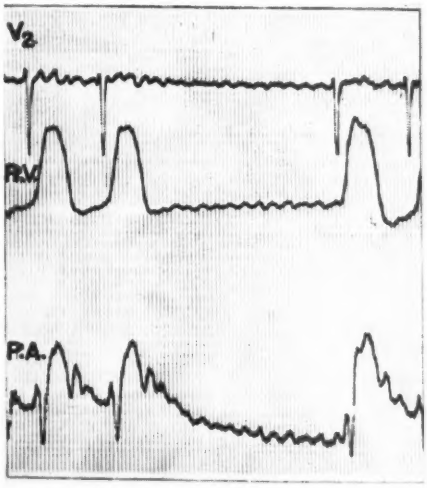


FIG. 6. Right ventricular (R.V.) and pulmonary artery (P.A.) pressure curves in a patient with flutter-fibrillation. Lead $V_2$ was used for timing but in all other respects the curves were recorded as in previous figures with the usual paper speed of 25 mm. per second.

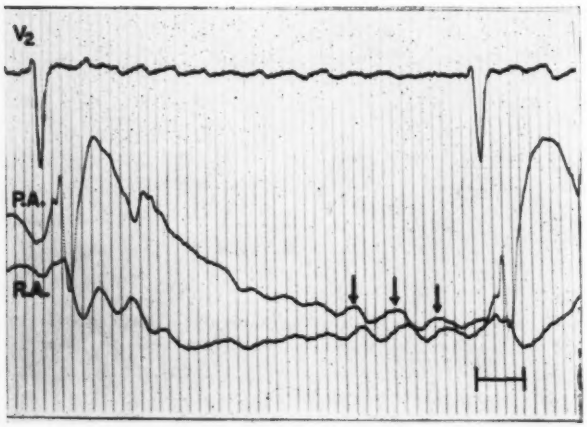


FIG. 7. Simultaneous pulmonary artery (P.A.) and right atrial (R.A.) curves in a patient with flutter-fibrillation. Lead $V_2$ was used with a rapid paper speed (75 mm. per second). The arrows indicate paired atrial systoles. The time interval between bars on lower right is 0.20 second.

indeed is less than the so-called "fibrillation threshold" which heralds the onset of disordered atrial activity according to Prinzmetal,[1] it is possible for the atrial chambers to respond with discrete mechanical systoles. It is interesting to note that individual atrial systolic waves on the pulmonary artery and right atrial curves resemble each other in height and contour. Indeed they can be paired as is indicated by arrows placed above three successive pairs of systoles in figure 7. From such a comparison it appears that the atrial event or "a" wave on the pulmonary artery curve precedes that on the atrial curve by 0.02 to 0.04 second rather than follows it by 0.12 second. The precedence of the atrial pressure wave inscription on the pulmonary artery curve can best be explained as a result of an impact produced by a left atrial contraction beginning before contraction of the right atrium. This sequence of contractions, which is the reverse of the normal, would imply a beginning of electrical atrial excitation on the left in this patient.

Another point of difference noted between atrial flutter and atrial fibrillation is that the pressure pattern of tricuspid insufficiency, so commonly observed in atrial fibrillation[6, 9, 10] even in the absence of elevated right atrial pressure,[6] rarely, if ever, occurs in atrial flutter. In figures 1, 4 and 5 the vertical lines through each atrial tracing indicate the onset of *ventricular* systole. In the patient with atrial fibrillation (right frame of fig. 4) there follows a pressure ascent characteristic of tricuspid regurgitation which is probably favored by the absence of a discrete mechanical atrial contraction.[11] In atrial flutter (fig. 1 and left frame of fig. 4) there is a fall in atrial pressure at this time, as occurs normally with the descent of the cardiac base, and hence there is no evidence of tricuspid insufficiency. In further support of the influence of atrial systole upon adequate closure of the A-V valves is the tracing in figure 5, where with flutter-fibrillation and discrete atrial systoles there is no tricuspid regurgitation.

Before leaving the discussion of the mechanical events in atrial flutter a word must be added regarding the measurement of atrial electric and mechanical relationship. It is unfortunate that our method of recording the electrical event was insufficiently sensitive to permit an accurate determination of the onset of each atrial excitation wave and therefore no attempt was made to determine the time interval between the two events.

*Blood Flow and Blood Volume.* Blood flow and blood volume were also measured in patients with atrial flutter. The influence of flutter upon cardiac output in nine cases is shown in table 1 and figure 8. One patient (Case 457), although subject to long bouts of flutter, had no other evidence of heart disease.

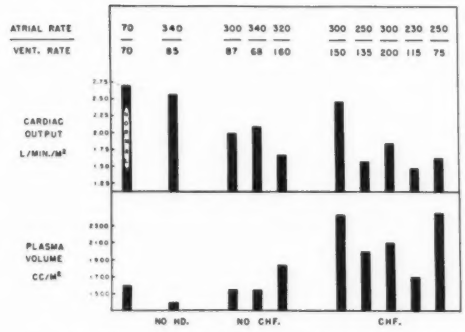
ATRIAL RATE
VENT. RATE
70 340 300 340 320 300 250 300 230 250
70 85 87 68 160 150 135 200 115 75
CARDIAC OUTPUT L/MIN./M²
APPARENT
PLASMA VOLUME CC/M²
NO HD. NO CHF. CHF.

FIG. 8. Diagram illustrating values obtained for cardiac output and plasma volume in each of nine patients in atrial flutter. The atrial and ventricular rates of each patient appear at the top of the diagram.

Of the eight cardiac patients, three (Cases 684, 777, 324) had no signs of congestive failure, while the remaining five, pulmonary and peripheral congestion were present at the time of study. The level of cardiac output was within normal limits in the subject without evident heart disease and was considerably reduced in all cardiac patients with or without congestive failure. The plasma volume, measured by dye T-1824, was increased in the five patients with congestive failure (Cases 405, 542, 477, 695, 619) as well as in one subject (Case 324) in whom failure had only very recently been relieved.

In order to learn to what extent the arrhythmia contributed to the reduction in blood flow, five patients were observed before and after conversion to normal sinus rhythm. The first three subjects (table 2 and fig. 9) had no congestive failure at the time of either study while the last two (Cases 542, 695) were in failure only during atrial flutter. The drugs utilized to produce conversion from atrial flutter to sinus rhythm were either quinidine (Cases 324, 777) or digitalis bodies (Cases 542, 684), or a combination of both (Case 695). At the time of restudy quinidine had in all instances been stopped while in two patients (Cases 542, 695) Digoxin was being continued. Since the oxygen consumptions and respiratory gas exchange ratios of the two studies in each patient are comparable (the greatest change in oxygen consumption between two studies in the same patient was 11 cc. per square meter of body surface area and in respiratory gas exchange ratios was 0.11) and indicated a similar basal state, one can conclude that in all instances after conversion, the resting cardiac output rose significantly (table 2). Obviously digitalization and relief of congestive failure must have contributed to a rise in cardiac output in the last two subjects shown in table 2 and figure 9 (Case 542, 695), but in the first three, these factors were not operative as they had not been in failure and medications if any were identical in each study. Moreover in two of these three there was little change in ventricular rate before and after conversion and hence no real difference in ventricular diastolic filling time. This suggests the possibility that atrial flutter per se was contributing to the reduced blood flow, perhaps because continuous atrial contractions impeded venous inflow.

*Lesser Circulation Pressures in Atrial Flutter.* With regard to pressures, these were in general within normal limits in the lesser circuit in those patients in atrial flutter without congestive failure (table 1), while brachial arterial pulse pressures tended to be small whenever the ventricular rate was rapid even if failure was absent (Case 324). It is interesting to contrast the type of pulmonary hypertension these patients with atrial flutter develop in the presence of right and left ventricular failure, with that shown by patients in sinus rhythm also in heart failure. In table 3 and figure 10 the level of pulmonary hypertension and the pulmonary artery pulse pressure are depicted in three groups of individuals in clinically comparable degrees of failure, who have atrial flutter, atrial fibrillation and sinus rhythm, respectively. The average pulse pressure for each group is encircled in figure 10. It is clear that with atrial flutter there is a much lower level of hypertension and a smaller pulse pressure than with sinus rhythm. The subjects with atrial flutter resemble those with atrial fibrillation in these respects.

This contrast in lesser circulation pressures is further emphasized by comparing the response to Digoxin in two patients in congestive failure, one with atrial flutter, the other with sinus rhythm, whose increases in

TABLE 2.—*Hemodynamic Data in Five Patients with Atrial Flutter Converted to Sinus Rhythm*

| Case | State | AR:VR (beats/min.) | Card. Output (L./min.) | Card. Index (L./min./M.² BSA) | Stroke Vol. (cc) | $O_2$ Consump. (cc./min./M.² BSA) | R.Q. | AV diff. (vol. %) | Arterial blood $O_2$ | | Pressures in mm. Hg | | | TBV (cc./M.² BSA) | PV (cc./M.² BSA) | H'crit. (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Cont. (vol. %) | Sat. (%) | Brachial art. s/d, m | Pulmon. art. s/d, m | Rt. vent. d | | | |
| Normal | | 70:70 | 5.50 | 3.12 | 70 | 131 | 0.80 | 4.2 | | 96 | 120/70, 90 | <30/10, 15 | <5 | 2750 | 1500 | 45 |
| #684 | A. Fl. | 300:87 | 3.72 | 2.00 | 43 | 148 | 0.74 | 7.4 | 19.7 | 98 | 126/77, 106 | 20/6, 11 | 4 | 2730 | 1369 | 50 |
| | NSR | 58:58 | 4.71 | 2.49 (+25%) | 81 | 137 | 0.82 | 5.5 | 18.6 | 94 | 165/75, 109 | 20/10, 14 | 5 | 2842 | 1485 | 48 |
| #777 | A. Fl. | 340:68 | 3.74 | 2.10 | 55 | 126 | 0.90 | 6.0 | 17.6 | 96 | 187/97, 128 | 26/14, 19 | 4 | 2572 | 1545 | 42 |
| | NSR | 66:66 | 4.98 | 2.75 (+31%) | 76 | 116 | 0.87 | 4.2 | 14.8 | 92 | 173/81, 118 | 33/17, 24 | 2 | 2834 | 1803 | 38 |
| #324 | A. Fl. | 320:160 | 2.59 | 1.67 | 16 | 122 | 0.89 | 7.3 | 14.0 | 81 | 102/74, 82 | 26/—, — | 0 | 3460 | 1840 | 47 |
| | NSR | 65:65 | 3.87 | 2.50 (+50%) | 60 | 115 | 0.78 | 4.6 | 13.4 | 92 | 103/63, 78 | 27/12, 16 | 0 | 3680 | 2140 | 42 |
| #542 | A. Fl. CHF | 250:135 | 2.60 | 1.58 | 19 | 142 | 0.75 | 9.0 | 16.0 | 97 | 116/93, 102 | 52/36, 43 | 15 | 3660 | 2000 | 45 |
| | NSR | 88:88 | 3.59 | 2.32 (+47%) | 41 | 132 | 0.82 | 5.7 | 16.2 | 92 | 93/63, 79 | 29/14, 20 | 0 | 3552 | 1867 | 47 |
| #695 | A. Fl. CHF | 230:115 | 2.56 | 1.48 | 22 | 117 | 0.81 | 7.9 | 16.1 | 89 | 128/90, 105 | 32/22, 26 | — | 3150 | 1698 | 46 |
| | NSR | 67:67 | 3.41 | 2.08 (+41%) | 51 | 110 | 0.80 | 5.3 | 17.4 | 99 | 138/67, 93 | 27/12, 18 | 2 | 2474 | 1400 | 43 |

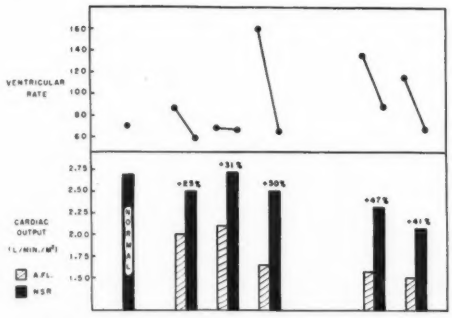


FIG. 9. Diagram illustrating cardiac output in five patients with atrial flutter subsequently converted to sinus rhythm. Reading from left to right, the first three patients did not have congestive failure at the time of study, while failure was present in the last two during atrial flutter.

TABLE 3.—*Pulmonary Artery Pulse Pressure, Stroke Volume and Ventricular Rate in Atrial Flutter, Atrial Fibrillation and Normal Sinus Rhythm in Congestive Heart Failure*

| Case | Press. in mm. Hg Pulmon. Art. s/d, m | pulse press. | Stroke Vol. (cc.) | Vent. Rate | Plasma Vol. (cc./M.²) |
|---|---|---|---|---|---|
| **Atrial Flutter in Congestive Heart Failure** | | | | | |
| *343 | 24/19, 21 | 5 | — | 150 | — |
| *477 | 22/16, 17 | 6 | 17 | 200 | 2110 |
| *695 | 29/19, 22 | 10 | 22 | 115 | 1698 |
| *619 | 32/22, 26 | 10 | 38 | 75 | 2480 |
| *542 | 52/36, 43 | 16 | 19 | 138 | 2000 |
| **Atrial Fibrillation in Congestive Heart Failure** | | | | | |
| *806 | 37/26, 32 | 11 | 12 | 163 | 1763 |
| *453 | 33/21, 27 | 12 | 25 | 125 | 1430 |
| *437 | 26/13, 19 | 13 | 22 | 129 | 2090 |
| *799 | 37/24, 29 | 13 | 38 | 117 | 1623 |
| *544 | 43/28 35 | 15 | 27 | 120 | 3320 |
| *682 | 41/21, 29 | 20 | 23 | 119 | 2440 |
| *794 | 36/14, 26 | 22 | 33 | 84 | 2003 |
| *688 | 61/38, 45 | 23 | 35 | 133 | 2347 |
| **Normal Sinus Rhythm in Congestive Heart Failure** | | | | | |
| *781 | 24/22, 26 | 12 | 37 | 110 | 2079 |
| *647 | 35/19, 24 | 16 | 64 | 92 | 2317 |
| *519 | 59/36, 48 | 23 | 29 | 114 | 1940 |
| *616 | 56/25, 39 | 31 | 48 | 98 | 2145 |
| *569 | 76/44, 60 | 32 | 33 | 115 | 1860 |
| *625 | 68/31, 45 | 37 | 30 | 90 | 2330 |
| *612 | 79/42, 57 | 37 | 33 | 106 | 1882 |

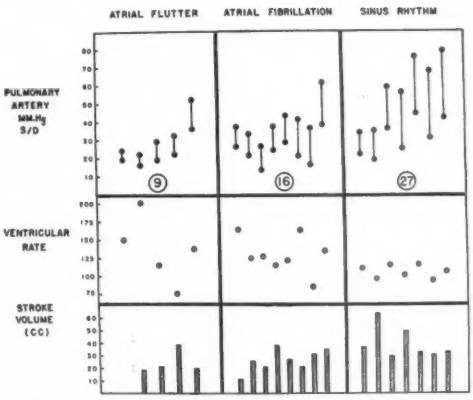


FIG. 10. Diagram illustrating the level of pulmonary hypertension and pulmonary artery pulse pressure, together with ventricular rate and stroke volume, in three groups of patients in congestive heart failure, who have, respectively, reading from left to right, atrial flutter, atrial fibrillation and sinus rhythm. The average pulse pressure for each group is encircled. Each symbol refers to a single patient.

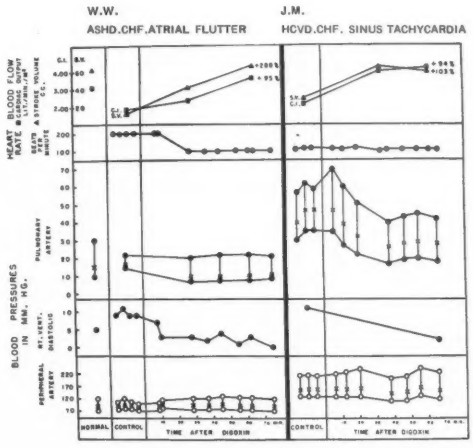


FIG. 11. Graphic representation of the hemodynamic findings in two patients (W. W., case 477 on the left, J. M. on the right) before and after the intravenous administration of Digoxin. For discussion see text. In this and subsequent figures, triangles = stroke volume; squares = cardiac index; target dots = heart rate; closed circles = pulmonary artery systolic and diastolic, and right ventricular end diastolic pressures; open circles = brachial artery systolic and diastolic pressures; cross marks = mean pressure. The normal values are plotted in the first vertical column.

TABLE 4.—*Hemodynamic Data Before and After Intravenous Administration of Digoxin in Four Patients With Atrial Flutter*

| Case | State | AR:VR (beats/min.) | Card. Index (L./min./M.² BSA) | Stroke Vol. (cc.) | $O_2$ Consumpt. (cc/min./M.² BSA) | R.Q. | AV diff. (vol. %) | Arterial blood $O_2$ | | Pressures in mm. Hg | | | TBV (cc./M.² BSA) | PV (cc./M.² BSA) | Hemato-crit. (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Cont. (vol. %) | Sat. (%) | Brachial art. s/d, m | Pulmon. art. s/d, m | Rt. vent. d | | | |
| #542 | Control | 250:135 | 1.58 | 19 | 142 | 0.75 | 9.0 | 16.0 | 97 | 116/93, 102 | 52/36, 43 | 15 | 3660 | 2000 | 45 |
| | After Digoxin* | 250:125 | 2.23 (+41%) | 30 (+58%) | 147 | 0.77 | 6.6 | 15.3 | 97 | 133/89, 104 | 55/27, 38 | 6 | — | — | — |
| #695 | Control | 230:115 | 1.48 | 22 | 117 | 0.81 | 7.9 | 16.1 | 89 | 128/90, 105 | 32/22, 26 | — | 3150 | 1698 | 46 |
| | After Digoxin* | 228:57 | 1.84 (+25%) | 45 (+105%) | 131 | 0.80 | 7.1 | 15.4 | 89 | 162/80, 106 | 31/17, 24 | — | — | — | — |
| #477 | Control | 300:200 | 1.85 | 17 | 122 | 0.89 | 6.6 | 18.9 | 95 | 106/81, 87 | 22/16, 17 | 9 | 3930 | 2110 | 46 |
| | After Digoxin‡ | 300:100 | 3.60 (+95%) | 66 (+288%) | 119 | 0.91 | 3.3 | 18.6 | 95 | 127/76, 98 | 19/9, 10 | 4 | — | — | — |
| #619 | Control | 250:75 | 1.62 | 38 | 131 | 0.92 | 8.1 | 19.8 | 97 | 121/84, 96 | 35/23, 28 | 21 | 5360 | 2480 | 53 |
| | After Digoxin† | 250:60 | 1.97 (+22%) | 58 (+53%) | 139 | 0.94 | 7.0 | 19.5 | 98 | 126/76, 95 | 31/18, 22 | 16 | — | — | — |

* 50 minutes after 1.25 mg. Digoxin intravenously.
† 64 minutes after 1.00 mg. Digoxin intravenously.
‡ 65 minutes after 1.50 mg. Digoxin intravenously.

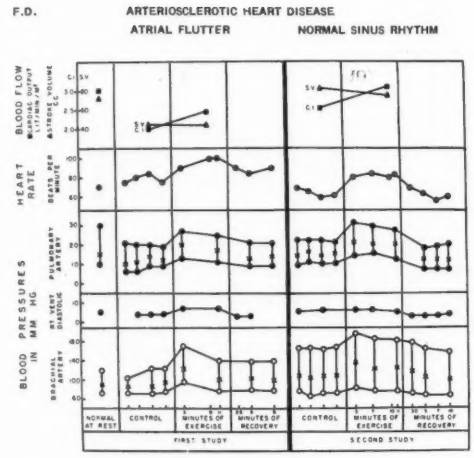


FIG. 12. Graphic representation of the hemodynamic findings in patient 684 (F. D.). At the time of the first study, he was in atrial flutter but was in sinus rhythm at the time of the second study. For discussion see text.

cardiac output after the glycoside was administered were approximately of the same magnitude and achieved much the same level of flow. In the patient with atrial flutter (W. W., Case 477), on the left in figure 11, who is representative of four so studied (table 4), the pulmonary artery pulse pressure widened, with a drop in diastolic to normal levels as the ventricular rate slowed and stroke volume increased. The rise in stroke volume and fall in diastolic pressure were evidences of better left ventricular emptying. In the patient (J. M.) in sinus rhythm, on the right, who had no change in ventricular rate, there was a drop in both phases of pulmonary pressures from a much higher level than was shown by the patient with flutter, without change in pulse pressure.

The small pulse pressure in the pulmonary artery during atrial flutter with congestive failure can be explained, at least in part, on the basis of a very small stroke volume (table 1 and fig. 10). It is more difficult to understand the mild degree of pulmonary hypertension in the presence of heart failure. In the flutter cases there may be a smaller pulmonary blood volume but why this should be true is a matter of speculation and impossible of measurement at present. Total blood volumes were comparable in all three groups in table 3 and figure 10. Perhaps venous inflow to the heart is impaired in atrial flutter by the continuous right atrial contraction, a mechanism which would tend to reduce the amount of blood entering the lesser circulation and result in a redistribution of blood in the peripheral venous bed. Under such circumstances, even if in the sequence of events initiating congestive failure, the left ventricle fails before the right, a relatively smaller amount of blood would accumulate in the pulmonary vascular bed than accumulates there in failure with sinus rhythm, since right ventricular inflow is already reduced by the fluttering atria. It is interesting that in another instance of the congested state accompanied by a small pulmonary artery pulse pressure and a low level of pulmonary hypertension, namely, chronic constrictive pericarditis, the absence of heterodynamism has also been postulated.[12, 13] In congestive failure occurring with sinus rhythm, when the left ventricle fails first and there is no impairment of the right ventricular inflow, there would be a much more marked temporary inequality or hetero-

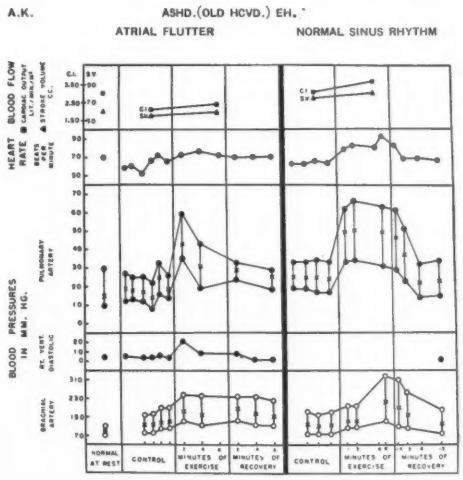


FIG. 13. Graphic representation of the hemodynamic findings in patient 777 (A. K.). At the time of the first study he was in atrial flutter but was in sinus rhythm at the time of the second study. For discussion see text.

dynamism of both ventricular outputs and hence a greater augmentation in pulmonary blood volume, more distention of the pulmonary vascular bed, and as a consequence of this a higher pulmonary hypertension and pulse pressure.

*Performance During Exercise.* The cardiocirculatory studies in flutter so far presented have been made at rest. How do these individuals behave under the stress of a mild exercise and does conversion to sinus rhythm alter their performance? Two patients who had never had any symptoms or signs of failure serve to elucidate these points. The first man (Case 684, tables 1, 2, and fig. 12) had a normal sized heart and while in atrial flutter had a subnormal increase in cardiac output in response to exercise (480 cc. per 100 cc. increase in oxygen consumption). After conversion to sinus rhythm the rise in cardiac output during exercise increased somewhat but was still probably subnormal (630 cc. per 100 cc. increase in oxygen consumption) even though the level of resting cardiac output was higher. In neither instance did lesser circuit pressures reach abnormal levels during exertion, indicating that there was no evidence of ventricular stress[6] at this time. Brachial artery pulse pressure was considerably greater after conversion to sinus rhythm. One could say that apart from a limitation in blood flow, this man did not have markedly deranged hemodynamics. The other patient Case 777 (tables 1, 2, and fig. 13), who had an enlarged left ventricle, also had a subnormal increase in blood flow during exercise. Furthermore he developed pulmonary artery and right ventricular diastolic hypertension on effort. The appearance of this hypertension suggests that the left and right ventricles were operating under strain and might even be considered to be failing during exertion, although the elevated pressures declined rapidly during recovery. The large venous return to the right heart, which occurs initially during leg exercise in the supine position, might cause a transient heterodynamism of both ventricles with consequent increase in pulmonary blood volume, resulting in a reduction in distention of the pulmonary artery and pulmonary hypertension with a wide pulse pressure. The large venous return would have thereby overcome the impedance to atrial inflow offered at rest by the fluttering right atrium. In this subject, as in the other, circulatory performance as measured was not altered by conversion to sinus rhythm, except for the higher level of resting cardiac output, suggesting that the failure or inadequacy of the ventricular myocardium remained as a primary defect despite the change in rhythm.

## Summary and Conclusions

In summary, data obtained in 12 patients with atrial flutter, using the cardiac catheterization technic, indicate that atrial flutter was associated with a low cardiac output in those 11 subjects with intrinsic heart disease. Furthermore the resting level of blood flow increased somewhat when the cardiac mechanism of five patients with atrial flutter was converted to sinus rhythm. In two cardiac patients the response to exercise in flutter was little different as compared with their performance in sinus rhythm.

Lesser circulation pressures in the absence of heart failure were not abnormal in this arrhythmia. In general, a small pulmonary artery pulse pressure and mild pulmonary hypertension characterized the patients with atrial flutter in congestive failure in contradistinction to patients with sinus rhythm and congestive failure.

Tricuspid insufficiency did not occur in atrial flutter in contrast to its almost constant appearance in atrial fibrillation.

Finally, atrial systolic pressure waves associated with each electric flutter wave were ubiquitously present in all lesser circulation pressure curves. The exact mechanism producing these waves in the large vessels invites further study.

## Summario in Interlingua

Datos obtenite per medio de catheterisation cardiac ab 12 patientes con flutter atrial indica que le flutter atrial esseva associate con un basse volumine-minuta del corde in le 11

casos con intrinsec morbo cardiac. Etiam, le fluxo sanguinee in stato de reposo se augmentava alique quando le mechanismo cardiac de 5 patientes con flutter atrial esseva convertite in rhythmo sinusal. In duo patientes cardiac le responsa a exercitio in flutter non differeva grandemente de lor modo de action in rhythmo sinusal.

In le absentia de dysfunctionamento cardiac, le pressiones del circulation minor non esseva anormal in iste genere de arrhythmia. In general, un basse pression pulsari del arteria pulmonar e leve grados de hypertension pulmonar characterisava le patientes con flutter atrial in dysfunctionamento congestive e differentiava iste patientes, ab illes con rhythmo sinusal e dysfunctionamento congestive.

Insufficientia tricuspide non occurreva in flutter atrial. Isto contrasta con le facto que insufficientia tricuspide es quasi semper presente in fibrillation atrial.

Finalmente, undas de systolic pression atrial associate con cata unda de flutter electric esseva presente ubique in omne curvas del pression in le circulation minor. Le exacte mechanismo que produce iste undas in le grande vasos invita studios additional.

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# Echinococcus Disease of the Left Ventricle

## A Clinical, Radiologic and Electrocardiographic Study

*By* Eduardo Joaquín Canabal, M.D., César V. Aguirre, M.D., Jorge Dighiero, M.D., Joaquín Purcallas, M.D., José M. Baldomir, M.D. and Carlos V. Suzacq, M.D.

The subject of echinococcus disease of the left ventricle is discussed from the clinical, radiologic, and electrocardiographic point of view. Up to the present very few cases of this condition have been reported in the world literature. In most instances the diagnosis has been made by postmortem examination. The diagnostic criteria presented in this paper may be helpful in the recognition of this disease which, if treated by surgery, may be another form of "reversible" heart disease.

ALTHOUGH echinococcus disease has a high incidence in many parts of the world and is therefore not rare, localization of this parasitic disease within the heart walls has not been recognized very often. In the vast majority of recorded cases a correct diagnosis of the condition was only made at postmortem examination. Prior to the publication of this paper surgery has been attempted in very few cases and the results have been rather discouraging because the patients came to operation in the late, complicated stages of the disease in most instances.

Diagnosis of this rare disease of the heart is of more than academic interest. Our experience in the early recognition and subsequent successful treatment of three consecutive cases of echinococcosis of the left ventricle prior to the occurrence of any complication has emphasized to us the importance of this disease which is less uncommon than has been thought.

In this communication we wish to discuss the clinical, radiologic and electrocardiographic features of uncomplicated echinococcosis of the left ventricle.

### Case Report

*Case 1.* P. S. was a 43-year-old farmer.[1] In 1950 a round mass in the left lung field, which apparently fused with the cardiac shadow, was discovered by radiologic examination. One year later the abnormal mass was somewhat larger. In August 1951 he was admitted to Professor Dr. V. Armand-Ugon's surgical service (Colonia Gustavo Saint-Bois, Montevideo) for further study.

His past history and family history were noncontributory. He gave no history suggesting illness; he complained of no symptoms attributable to a cardiac disease or to hydatid anaphylaxis. On physical examination of his heart no murmurs or thrills were elicited. Cardiac size was normal by percussion. Blood pressure was 130/80. The pulse was regular, at a rate of 80 beats per minute. No signs of congestive heart failure or acute pericarditis were present. Routine laboratory examinations were essentially normal.

Roentgenograms of the chest revealed marked prominence in the outline of the left ventricle in the posterior-anterior projection (fig. 1). A round mass of uniform density, superimposed on the heart shadow, was visible in the left lateral projection. By fluoroscopy this prominence had neither systolic expansion nor paradoxical contraction. No calcification was seen within, or at the edges of the abnormal cardiac shadow. Lung fields were clear and the diaphragm moved freely. A tomographic examination showed that the deformity was located mainly at the posterior region of the left ventricle. Angiocardiography showed a normal outline of the cavity of this structure.

An electrocardiogram (fig. 2) showed a sinus mechanism with a rate of 75 beats per minute and left axis deviation in a horizontal heart. T waves were inverted in leads I and $aV_L$ and upright in $aV_R$. In the precordial leads, T waves were inverted from position 5 to position 9, inclusive, with a maximal inversion in $V_6$ and $V_7$. Isoelectric RS-T segments were present in all leads. There was slight slurring of R waves in the precordial leads from $V_4$ on. No abnormal Q waves were present.

On Sept. 15, 1951 the patient was operated upon by Prof. Armand-Ugon, after anesthesia with sodium pentothal, cyclopropane, ether and oxygen. A left anterolateral thoracotomy at the fourth left intercostal space with no rib resection was per-

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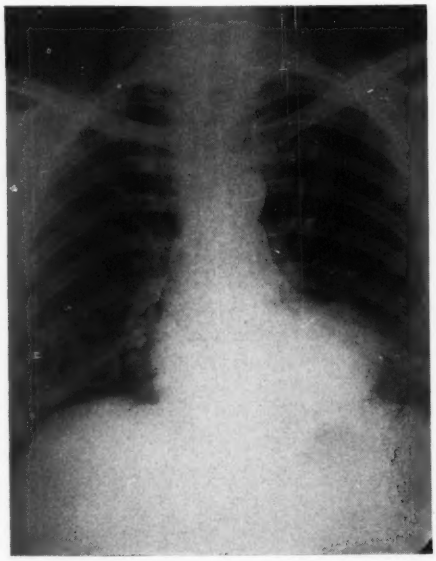

FIG. 1. Case 1. Roentgenogram in anterior-posterior position. There is a clear cut bulge in the outline of the left ventricle.

formed. A multilocular hydatid cyst localized at the posterolateral region of the left ventricle and protruding into the pericardial cavity was found. There were no pericardial adhesions at all in the region where the cyst bulged from the surface of the heart. The left ventricular wall underlying the cyst was of normal thickness. Through a cystostomy the hydatid membrane, seven daughter cysts, and a good amount of normal looking hydatid fluid were removed. After resection of a portion of excessive adventitia and irrigation of the internal surface of the cyst with ether, the adventitia and the pericardium were closed with interrupted sutures. The chest wall was closed in layers.

After developing a moderate left pleural effusion, the patient made an uneventful recovery and was discharged from the hospital 18 days after operation. He has been followed at regular intervals since discharge. The heart shape returned to normal immediately after operation. There has remained a persistent elevation of the left diaphragm. An electrocardiogram taken one year after operation was not changed from the preoperative tracing.

*Case 2.* P. C., a 24-year-old farmer,[3] was admitted to Professor Dr. P. Larghero-Ybarz's surgical service (Pasteur Hospital, Montevideo) because of a left paracardiac round mass discovered on fluoroscopic examination after an acute illness diagnosed as acute bronchitis. His past history and his family history were noncontributory. On physical examination the heart sounds were normal and neither murmurs nor thrills over the precordial region were present. Blood pressure was 100/60. The pulse was regular at a rate of 65 beats per minute. Heart size by percussion was within normal limits. The patient was in no distress and there were no signs of cardiac failure. The lungs were clear. Laboratory tests were normal, except for an early, as well as a late, positive intradermal Casoni test.

The electrocardiographic report (fig. 3) was as follows: sinus rhythm, at a rate of 60 beats per minute; heart in vertical position; symmetrically inverted T waves in leads I and $aV_L$ and upright T waves in $aV_R$; very deep and acute inversion of T waves in leads $V_3$ through $V_6$, inclusive; slightly inverted T waves in $V_7$ and diphasic T waves in $V_2$; very small R waves in leads $V_1$ to $V_4$ inclusive, becoming suddenly higher in $V_6$ and $V_7$; QRS complexes of the r-s-r′ type and of very low voltage in

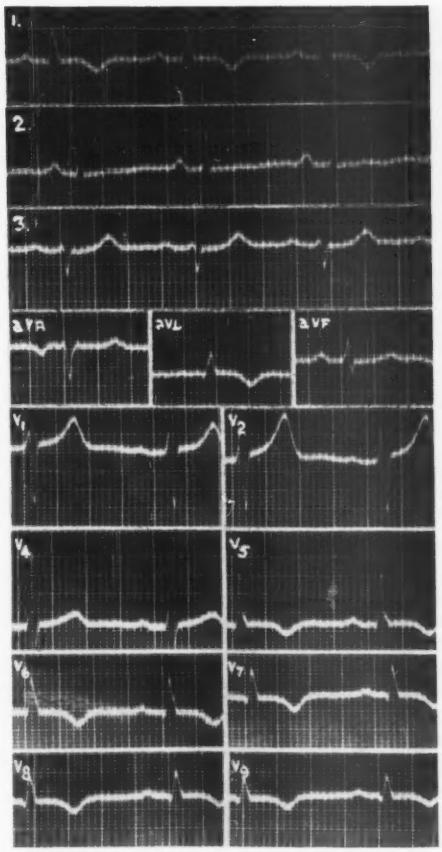


FIG. 2. Case 1. Preoperative electrocardiogram. Note T wave inversion in leads I, $aV_L$ and $V_3$ through $V_9$. There also is slight slurring of R waves from $V_4$ on.

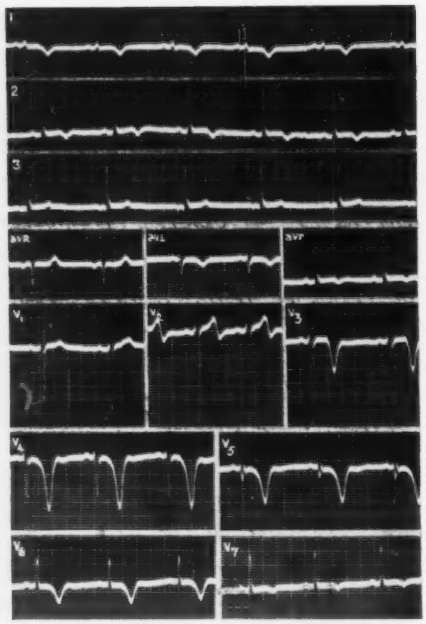

FIG. 3. Case 2. Preoperative electrocardiogram. Note the "coronary" type inversion of T waves in positions 3, 4, 5, and 6 of the precordial leads, as well as the marked reduction of R waves in some of these leads.

$V_5$; absence of abnormal Q waves, as well as of abnormal displacements of the RS-T segments in all leads. Precordial leads taken at the level of the third intercostal space[3, 4] recorded similar, but not so marked, changes. This electrocardiographic pattern, highly suggestive or diagnostic of an important degree of myocardial ischemia of the anterolateral wall of the left ventricle in a 24-year-old man with no past or present history of heart disease, aroused our interest immediately.

Roentgenograms of the chest showed a clear cut deformity of the cardiac shadow in the apical region, best seen in the right anterior oblique position. Some areas of calcification at the level of the left ventricle were also present (fig. 4). A tomographic study, performed by Drs. E. R. Zerboni and A. Gorlero-Armas, confirmed the presence of both the ventricular deformity and spotty calcification. Angiocardiograms were made, using a Fairchild camera and 40 cc. of a 75 per cent solution of Neo-Iopax. In three consecutive exposures of the levoangiocardiogram taken at one-second intervals, obliteration of the outline of the left ventricular cavity at its apical region was demonstrated (fig. 5).

In view of the history, the radiologic findings, the positive Casoni test and, last but not least, our previous experience with echinococcosis of the heart[1, 5], we felt that the electrocardiographic changes could be caused by a hydatid cyst located at the anterolateral region of the left ventricle.

Because of the electrocardiographic findings (deep inversion of the T waves and very small R waves in some precordial leads) and the angiocardiograms, we were able to warn the surgeon before

FIG. 4. Case 2. Roentgenographic left lateral view of the chest. Note the round shadow superimposed to the cardiac silhouette and calcifications.

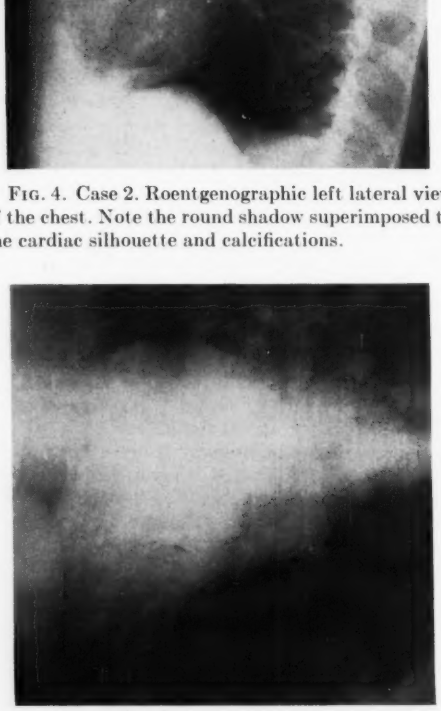

FIG. 5. Case 2. This levoangiocardiogram shows a clear amputation of the outline of the left ventricular cavity at its apical region.

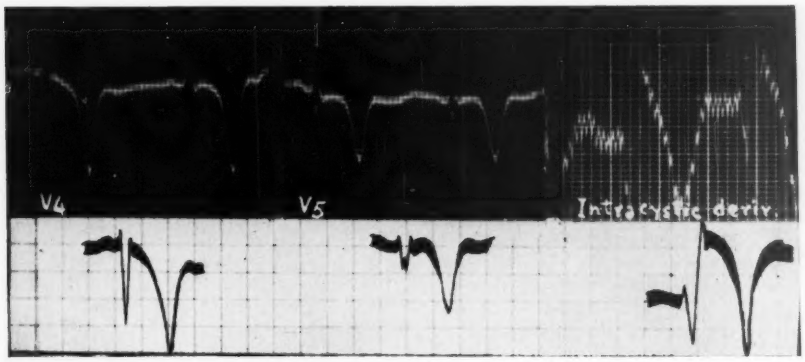


FIG. 6. Case 2. Comparative study of precordial leads, positions $V_4$ and $V_5$, and an intracystic lead recorded during operation. Note the low R waves and the elevated RS-T segments registered in the latter (see text).

operation of the great probability of extreme thinning of the wall of the left ventricle underlying the cyst.

Assistant Professor Dr. Luis M. Bosch-del-Marco operated upon this patient, performing a left anterior thoracotomy with resection of the fifth rib under general anesthesia. A 6 by 4 cm. oval mass located slightly above the apex of the left ventricle was found. There were firm adhesions of both pericardial layers at the region where the abnormal mass bulged from the heart surface. Having failed to obtain any substance from a tap through the adhesions, a rather ample incision was made on its surface. After cutting through a 2 cm. layer of fibrous tissue, a few fragments of a highly modified hydatid membrane and some quantity of caseous substance ("hydatid putty") were obtained from the cavity of the cyst. A finger introduced in this cavity failed to feel contractions of muscle fibers at its very bottom, but did detect the thinness of the myocardial wall beneath the cyst. An electrocardiogram made with an electrode inside the cavity of the cyst (fig. 6) showed very low R waves and elevated RS-T segments. Both findings were thus confirmatory of our prediction and demonstrated that the muscular layer beneath the cyst was thin, yet excitable. The cavity was emptied of all hydatid material, washed with ether and injected with 400,000 units of penicillin. The myocardial incision, as well as the pericardial sac, was closed with interrupted sutures. The thoracic wall was sutured in layers and two drains were left in the left anterior and posterior pleural sinuses.

The patient was discharged one month after operation and made an uneventful recovery. Serial postoperative electrocardiograms have shown slight improvement, but a marked degree of T-wave inversion and changes in the QRS complex has persisted.

*Case 3.* J. S. B., a 40-year-old housewife,[6] who had lived on a farm for a few years, was admitted to Professor Dr. P. Larghero-Ybarz's service (Pasteur Hospital, Montevideo) on Oct. 21, 1951, because of a second attack of acute cholecystitis. As she had had late toxemia of pregnancy with very high blood

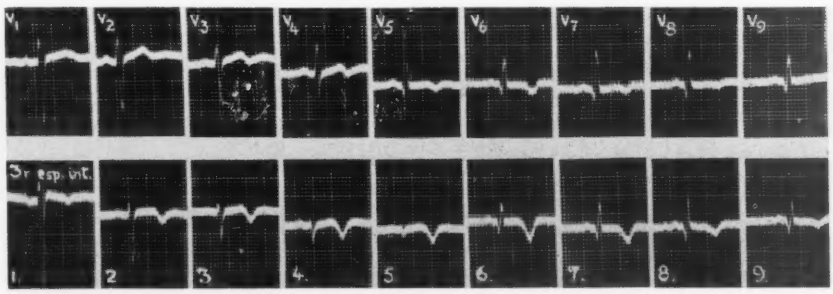


FIG. 7. Case 3. Comparative study of precordial leads taken at the standard positions and at the level of the third intercostal space, respectively. QRS and T wave changes are more obvious in the latter.

pressure, she was referred to our service for evaluation of her cardiovascular status.

On clinical examination, the heart sounds were found to be normal. Blood pressure was 130/90 and the pulse was regular at a rate of 65 beats per minute. On fluoroscopy we found a bulge at the upper part of the left ventricle. This deformity did not expand, but showed a line of marginal calcification. Because of these features a diagnosis of hydatid cyst of the left ventricle was made.

The principal electrocardiographic findings were: inverted T waves in leads I and $aV_L$; progressive reduction in amplitude of the R waves from $V_1$ through $V_3$; taller R waves from $V_5$ on; slight slurring of the R waves in some left precordial leads; isoelectric RS-T segments; diphasic T waves in $V_3$, $V_4$, $V_7$, $V_8$, and $V_9$ and inverted T waves in $V_5$ and $V_6$. Precordial leads made at the level of the third intercostal space showed (fig. 7): inversion of T waves in all positions, but most marked in positions 4, 5, 6 and 7; isoelectric RS-T segments; progressive diminution in amplitude of the R waves from V 1 through V 5 with return to a normal amplitude from position 6 on. On the basis of our previous experience, these changes were thought to be caused by a cyst located at the high lateral region of the left ventricle and a thin myocardial wall underlying the cyst, as was the case in the previous observation.

Drs. Zerboni and Gorlero-Armas' roentgenologic and tomographic studies revealed "an irregularly calcified image, highly suggestive of hydatid cyst, located at the superior region of the left ventricle" (fig. 8). Angiocardiography revealed a filling defect in the outline of the upper region of the left ventricular cavity facing the zone where marginal calcification was present. Laboratory examinations were all within the range of normal. Casoni's intradermal test was negative.

FIG. 8. Case 3. Tomography. Calcification of the ventricular bulge shows concentric distribution.

On Nov. 14, 1951 Professor Larghero-Ybarz performed a left anterior thoracotomy with resection of the fifth rib under general anesthesia. A hard, partially calcified, helmet-like mass adherent to the pericardium and bulging out from the surface of the high lateral region of the left ventricle was found. This mass turned out to be a degenerated hydatid cyst with a very thick and calcified adventitia. After puncture of the cyst that did not yield any fluid, an incision of the adventitia was made and a certain amount of caseous material was obtained after curettement of the cyst cavity. The internal layer of the adventitia showed patchy necrosis. The cavity of the cyst was carefully washed with hypertonic saline solution. Palpation of its base showed remarkable thinning of the muscular wall underlying it. After partial resection the adventitia was closed with interrupted sutures. The pericardium was closed in the same way. The thoracic wall was closed in layers.

The patient was discharged from the hospital 15 days after operation in good condition. She has been followed postoperatively at regular intervals. She is now doing very well and is quite active. The cardiac deformity disappeared. Serial electrocardiograms taken after operation show the same changes that were present before operation, although the T waves are now not so deeply inverted.

## DISCUSSION

According to Dévé[7-9] and most of the authors who have dealt with this disease, hydatid cyst of the heart is always single. The hexacanth embryo, after traversing both hepatic and pulmonary capillary networks, reaches the left heart chambers and passes through the coronary circulation to reach the myocardium of any one of the four heart chambers or the cardiac septa. In the course of a few weeks the hexacanth embryo becomes vesicular and grows at a rather quick rate. The hydatid vesicle, giving rise to a unilocular cyst, exerts pressure on the surrounding myocardial fibers which become more or less ischemic, depending on the degree of pressure caused by the parasite and the resistance of the cardiac tissue. As the cyst grows, the tissue reaction in the host leads to the formation of a fibrous capsule called adventitia, which shows cellular infiltration and becomes gradually thicker.

Due to the particular density of the myo-

cardium, the development of the hydatid cyst is restrained. This phenomenon is more obvious when the cyst is located in either ventricle. This is the reason why in most cases there is a reactive daughter cyst formation and/or why the primary cyst undergoes other changes such as degeneration or suppuration. When one or more of these changes take place, the adventitia becomes thicker, denser and even partially calcified and causes comparatively more harm to the surrounding myocardial structures.

The primary hydatid cyst shows a marked tendency to rupture either into one of the four heart chambers or into the pericardial sac. This accident gives rise to well known complications that we will not comment upon here in detail. While the pericardium usually reacts to a hydatid cyst by developing adhesions, the endocardium develops no reaction and is easily penetrated by the cyst.

Until rather recently it was thought that the primary cyst was more frequently lodged in the walls of the right heart chambers than in those of the left. In a review of this subject made in 1928, Dévé[7] pointed out that this concept was wrong and that there were comparatively more cases of primary hydatid cysts located in the wall of the left chambers, particularly the ventricle, than in the wall of the right chambers or in the cardiac septa. Dévé expressed the opinion that this was due to the fact that the left ventricle has a relatively richer coronary circulation.

The growth of a hydatid cyst within the myocardial wall of any one of the heart chambers usually produces a localized bulge in its silhouette, a feature which makes possible roentgenologic recognition of the disease. It should be pointed out that this localized deformity of the heart is readily detectable only when the hydatid cyst has reached a certain size. Medical literature abounds in cases[10-13] where cardiac cysts ruptured before causing a deformity of the organ. In some of these instances the diagnosis of echinococcosis of the heart was made only after recognition of some of its complications. Therefore early detection of localized deformities of the cardiac silhouette in echinococcosis of the heart is the only way of making an early diagnosis when surgery can cure the disease and prevent accidents and complications. This is particularly true, when we realize that *uncomplicated hydatid disease of the heart has no particular clinical picture.*

*Roentgenology* must be given credit in our various cases[1, 2, 5, 6, 14] and in some other cases [15, 16, 17] for first calling attention to the disease. *Fluoroscopy* represents a very important diagnostic method, because the deformity and calcifications may be discovered and studied in all projections. It usually gives very valuable information about the size, shape, and location of the abnormal mass, about its contour and about its movements. However, we feel that *kymography* may be much more accurate in the study of the latter.[18, 19, 20]

*Roentgenograms* taken in different projections permit a more detailed study of ventricular deformity and the importance, the location, and the extension of calcifications. As pulmonary hydatid cysts very seldom or never show calcification, every calcified shadow in the periphery of the heart, if not due to constrictive pericarditis, should suggest the possibility of a hydatid cyst. When spotty areas of calcification are seen in the cardiac shadow, one may also think of echinococcus disease, if calcification of the heart valves can be ruled out. Intramural fibromas may also calcify, but this disease is extremely rare.[21] *Tomography* usually gives very good information about the size, shape and location of the intramural cyst, as well as about the outline and position of the calcific zones, if present.

*Angiocardiography* has proved to be most helpful in the study of hydatid cysts of the left ventricle. Up to the moment of writing our first two papers on this subject[1, 2] we did not find bibliographic data relative to angiocardiography applied to the study of this condition. Although only our last three cases were studied by this method, we feel that this procedure gives valuable information when the hydatid cyst bulges into the left ventricular cavity; it is also particularly helpful in estimating the thickness of the myocardial wall underlying the cyst. If the hydatid vesicle is primarily located in the superficial layers of the myocardium (case 1), the layer of uninvolved

myocardium prevents the cyst from producing deformities of the ventricular cavity. If, on the other hand, the cyst is closer to the endocardial surface, the ventricular cavity may show localized deformities which are easily detectable by angiocardiography (cases 2 and 3). In such cases the surgeon must be extremely cautious in handling the cyst because the layer of myocardium underneath it is thin. Angiocardiography is also helpful in establishing the differential diagnosis between a hydatid cyst and an aneurysm of the left ventricle. Both diseases may cause a bulge in the silhouette of this cardiac chamber, but their angiocardiographic pattern is quite different.[22]

*Electrocardiography*, according to our recent experience[1, 2, 6, 14], represents a very reliable diagnostic method as far as echinococcus disease of the left ventricle is concerned.[23, 24, 25]

Looking at the preoperative tracings of our three cases (figs. 2, 3 and 7), we find several changes that are common to all of them:

(1) Inversion of T waves in leads I and $aV_L$.

(2) Upright T waves in lead $aV_R$ in two cases.

(3) Absence of abnormal Q waves in the standard, as well as in the precordial unipolar leads.

(4) Small R waves (cases 2 and 3) in those precordial leads taken from sites overlying that part of the left ventricular wall in which the cyst is implanted.

(5) Abrupt increase in amplitude of the R waves immediately beyond the above mentioned site.

(6) R waves of normal or nearly normal amplitude in the precordial leads in cases in which the hydatid cyst occupies only the most superficial layers of the myocardium of the left ventricle (case 1).

(7) Slight slurring of the QRS complexes in leads made from precordial positions overlying the cyst.

(8) Inversion of the T waves (of "coronary" type in some cases) in precordial leads which show changes in the QRS complexes.

(9) Absence of abnormal displacements of the RS-T segments in the standard, as well as in the unipolar limb and precordial leads, even in the positions where T-wave changes are most marked.

(10) A lesser degree of change in the QRS complexes and T waves in the precordial leads recording the potential variations of the peripheral regions of the cyst.

When a hydatid cyst of the left ventricle has not ruptured into the cavity of this chamber (as in our three cases), the subendocardial layers of the myocardium beneath the cyst remain excitable and the Purkinje network does not show changes worthy of comment. Therefore the excitation process in these fibers gives rise to R waves, whose amplitude depend on the thickness of the myocardial wall separating the cyst from the ventricular cavity. If the cyst is superficially located and has grown mainly toward the pericardial cavity, the R waves of the precordial leads made from positions on the chest wall immediately over the cyst will show a normal amplitude or a slight reduction in voltage (case 1, fig. 2). If, on the contrary, the cyst is more deeply located in the myocardium and an altered adventitia has caused comparatively more harm to the surrounding muscle fibers, the R waves in the precordial leads made from positions over the cyst are considerably smaller than normal (cases 2 and 3, figs. 3 and 7). At the same time there is a relative reduction of the voltage of the R waves in such cases, when compared with the amplitude of the other components of the QRS complex. When the precordial electrode is located over the peripheral zones of the cyst, the QRS complexes exhibit a normal amplitude. Thus, in cases in which the cyst pushes deeply into the myocardial wall, the voltage of the QRS complexes in multiple precordial leads give accurate information concerning its size. We believe that the low voltage of the R waves and the QRS complexes is caused by a reduction in thickness of the myocardial wall beneath the cyst and not by the presence of the cyst itself. This interpretation of the significance of the size of the R waves received some confirmation by comparison and agreement of the findings at operation and the electrocardiogram, as in cases 2 and 3. (See fig. 6.)

Because of the integrity of the myocardium

in the region underlying the cyst, the absence of abnormal Q waves and of intraventricular conduction defects is readily explainable.

There still remain to be explained the isoelectric RS-T segments and the inversion of the T waves. Echinococcosis of the heart is much more frequent in young than in elderly people. Therefore there is little likelihood that degenerative heart disease will exist concomitantly with echinococcosis. It is probable that electrocardiographic changes will only be caused by the cyst and its adventitia in the myocardial wall.

Although the cause of persistent elevation of the RS-T segments in ventricular aneurysm is not agreed upon,[26] a proposed explanation is that the elevation is caused by tension during systole at the junctional zone where fibrous replacement joins living myocardium. It seems to us that the same circumstances are present in echinococcus disease of the left ventricle with marked thinning of the myocardial wall; yet, as far as we know, no case of hydatid disease of the left ventricle has shown abnormal displacement of the RS-T segments, even after surgical removal of the cyst. Therefore, a sounder explanation for the elevation of the RS-T segments in ventricular aneurysm other than transient "injury" must be looked for. We feel that isoelectric RS-T segments in multiple precordial leads in cases of abnormal bulging in the outline of the left ventricle is a rather reliable sign, in addition to the absence of abnormal Q waves, in differentiating between echinococcus disease and ventricular aneurysm,[27] although it is known that not all the cases of the latter[28] show persistent elevation of the above mentioned segments.

Pathologic specimens of echinococcus disease of the heart, by demonstrating a process of ischemia and compression atrophy of the myocardial fibers in close relationship with the cyst, explain the inversion of the T waves in multiple precordial, as well as in standard and unipolar limb leads. This process of ischemia, caused by the cyst in the myocardial wall near the precordial electrode, is revealed by inverted T waves. The inversion of T waves is most marked in the leads made from sites on the chest wall over the center of the cyst and decreases gradually as the electrode registers the potential variations of the more peripheral zones (figs. 2, 3 and 7).

As we have found that changes in the T waves (chiefly in precordial leads) have been most helpful in the correct localization of the cyst, multiple precordial leads at different levels of the chest must be recorded in cases where echinococcus disease of the left ventricle is suspected. In case 3 (fig. 7) there were some changes in the QRS complexes and T waves in the standard precordial leads, but they were not so marked as those encountered at the level of the third intercostal space. This indicated that the cyst was located at the high lateral region of the left ventricle, but was sufficiently large to cause some changes even at the level of the fifth intercostal space.

It seems quite probable that in case 1 the precordial electrode only recorded the potential variations of an ischemic wall near it. In cases 2 and 3, where only a very thin muscular wall was interposed between the cyst and the ventricular cavity, the precordial electrode may have well recorded not only the "ischemia" pattern of the wall bearing the cyst but also the potential variations of the opposite wall. This would explain the deep inversion of the T waves, since we know that T waves produced by activation of the posterior wall are recorded as inverted waves in anterior chest leads. This deep inversion cannot be explained on the basis of disturbances in the repolarization process of the ventricular wall located near the recording electrode, because, if this were so, T waves should show a low amplitude just as the R waves in the same leads show low voltage. (See fig. 3, leads $V_3$, $V_4$, and $V_5$ and fig. 7, position 4, 5, and 6 of the precordial lead taken at the level of the third intercostal space.)

If this explanation seems suitable, one must then accept that the more marked the degree of T wave inversion in some precordial leads the thinner the muscular wall beneath the cyst in the left ventricular wall. This interpretation has been confirmed in all three of our cases by angiocardiography and by surgery. A case previously reported by two of us

(J. D. and E. J. C.)[5] and the case of Pérez Fontana and Sapriza[29] add support to this explanation. The latter authors have demonstrated that, if the cyst is quite superficially implanted in the myocardial wall, T-wave inversion may disappear some time (weeks or months) after operation.

Inversion of T waves in lead $aV_L$ may be interpreted as the result of transmission to the left arm of an altered repolarization process occurring in the left ventricle. If the hydatid cyst is located in the apical region of a vertical heart, T-wave inversion may be present in lead $aV_F$ instead of $aV_L$.

Positive T waves in $aV_R$ may either be the consequence of forward rotation of the apex (case 1) or of right ventricular cavity potentials (case 2) in a patient with inverted T waves in the precordial leads. T-wave changes in $aV_L$ and $aV_R$, in their turn, explain why these same waves are inverted in lead I.

Emphasis must be put on the definite superiority of multiple precordial leads in the study of cases suspicious of hydatidosis of the left ventricle. While in these leads the QRS complexes, RS-T segments and T waves may exhibit changes of diagnostic value, the standard, as well as the unipolar limb leads show changes which are present in a number of other cardiac conditions.

## Summary

(1) The clinical, electrocardiographic and radiologic features of three cases of echinococcus disease of the left ventricle, which were diagnosed correctly, localized accurately and operated upon thereafter successfully, are presented and discussed.

(2) Hydatid disease of the heart may remain latent for some time and give symptoms only when the myocardial cyst ruptures into a heart chamber or into the pericardial sac. Because of its latency, early recognition of this disease is only possible by radiologic examination of the chest and/or by electrocardiography.

(3) Fluoroscopic and roentgenologic examination may show a localized deformity, with or without marginal calcification, of the outline of the left ventricle. In some cases spotted areas of calcific density may be seen at the zone of implantation of the cyst in the myocardial wall. Angiocardiography may demonstrate localized deformities and filling defects within the ventricular cavity.

(4) A typical electrocardiographic pattern, yielding information concerning the position of the cyst and the thickness of the myocardial wall underlying it, is described.

(5) Early surgical intervention is strongly recommended as the only reasonable way of dealing with echinococcus disease of the left ventricle.

## Summario in Interlingua

1. Es presentate e discutite le characteristicas clinic, electrocardiographic, e radiologic de tres casos de morbo echinococcal del ventriculo sinistre le quales esseva correctemente diagnosticate, accuratemente localisate, e subseqeuntemente operate con bon successo.

2. Morbo hydatidic del corde pote remaner latente pro alicun tempore e exhibir symptomas solmente quando le cyste myocardial se rumpe e se discarga a in le camera cardiac o a in le sacco pericardial. A causa de su prolongate stato latente, le precoce recognition de iste morbo es possibile solmente per medio de examines radiologic del thorace e/o per medios electrocardiographic.

3. Le examine fluoroscopic e roentgenologic pote exhibir un deformitate local—con o sin calcification marginal—in le contorno del ventriculo sinistre. In alicun casos areas maculate de densitate calcific pote esser visibile in le zona de implantation del cyste e in le pariete myocardial. Angiocardiographia pote demonstrar deformitates local e defectos del replenamento intra le cavitate ventricular.

4. Nos describe un typic configuration electrocardiographic que provide information in re le position del cyste e le spissitate del subjacente pariete myocardial.

5. Nos sublinea le importantia de precoce identification del morbo. Isto es le sol methodo rationabile de attaccar casos de morbo echinococcal del ventriculo sinistre.

## Addendum

Since this paper was submitted for publication, we have studied six additional cases of uncomplicated hydatidosis of the left ventricle

All of them showed findings similar to those shown by the three cases presented in this paper.

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# The Heart Muscle and the Electrocardiogram in Coronary Disease

## III. A New Classification of Ventricular Myocardial Damage Derived from the Clinicopathologic Findings in 100 Patients (Part Two)

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NOTE: *In view of the length of this article, it is being published in two issues. This issue contains the Discussion and References. The September 1955 issue included the Introduction, Methods and Results. The synopsis of the article is repeated below.*—ED.

Methods, designed to study in detail the lesions resulting from coronary disease and to reconstruct accurately the form of all ventricular muscle lesions, have been applied to 100 consecutive electrocardiographed patients who were found to have at least one severe coronary narrowing. Reclassification of lesions into four categories was found necessary to deal with the patterns of damage disclosed. This approach permits conclusions regarding evolution of muscle damage, relationships of arterial obstruction to muscle damage distribution, and the significance of ischemia which would have been impossible otherwise. The value of the new classification for electrocardiography will be discussed in a subsequent section of the report.

### DISCUSSION

#### 1. *Representative Character and Peculiarities of the Statistical Sample*

We believe the most important feature of this study to be the demonstration that patients with obstructive coronary disease may have a number of basically different myocardial damage situations, which can be defined simply and unambiguously under four categories. All our patients with muscle damage could be assigned to one or another of these with little difficulty. The exact percentage composition of our sample is of course of little importance, since it might vary considerably for another hundred cases. It is noteworthy, however, that all four basic situations proved to be *common* and therefore demanding of clinical and investigative consideration.

Certain deficiencies in the size and composition of our sample should be kept in mind. A major distributional distortion must have been introduced by the requirement that all the patients be electrocardiographed. Undoubtedly an unselected necropsy series of patients over the age of 40 years would have yielded a larger percentage of scars, especially the small regional types that were not major causes of death. Indeed, our preliminary report[1] included 35 such scars, more than half of which were discarded from the present sample because they lacked electrocardiographic documentation. Study of a series of patients with typical uncomplicated anginal syndromes who died of some "noncoronary" cause would be of great interest. Only a few of our patients (all in group I) are in this category. Certain widespread damage situations are not well enough represented, notably, hearts with small, regional scars plus acute, subendocardial infarction confined to another region; for they must represent a common transitional stat

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between group I and group III presumably not as often lethal as other states. *Two* large (transmural) lesions in the same heart, each with a regional distribution, were found in only two instances. However, in view of the fact that at necropsy 10 per cent of the hearts contained a large regional scar and none had acute damage in any *other* region, we thought that more than one large (transmural) lesion in the same heart was an actually uncommon situation rather than a failure of our sample to be representative.

We would not expect the various myocardial situations here described to have similar frequencies if based on series of routine autopsy protocols, however painstaking or voluminous. Common errors in routine necropsies are failure to find more than one portion of the widespread or multiple scars of group III patients; missing altogether the widespread acute lesions of group IV patients or, having found only part of the necrosis, describing it as localized damage; and failure to discern the small subendocardial posterior, posterolateral and lateral scars that in our experience were the earliest and commonest of healed lesions. Such errors would automatically lead to exaggeration of the size of group II with its "anterior" and "posterior" massive lesions, which are almost never missed and seldom misinterpreted; to shrinkage of group I with its small subendocardial "posterior" and "lateral" single lesions (especially likely because as a rule these patients died of something besides coronary disease); and to replacement of groups III and IV by dismissive mention of "diffuse" scarring or "multiple lesions" considered to be of a complexity too extreme to repay meticulous study.

*An unexpected and important finding was the peculiarly high or low incidence of certain types and combinations of muscle damage, in contrast to the rather even distribution of stenotic and occlusive coronary lesions.* These phenomena were characteristic of the sample as a whole and not a consequence of our method of grouping the cases. However, the classification derived from our data brought out certain of these peculiarities of muscle lesion distribution very strikingly.

We have noted that small regional lesions were much commoner in the right and the left circumflex coronary regions than in the anterior descending region, whereas "anteriors" were by far the commonest type of large regional lesion. In the whole sample, however, anterior damage was no less common than damage in other locations. From this, it followed that "small" anterior lesions strongly tended to be associated with earlier or coëval damage in at least one other region. Perhaps the simplest general summation of these phenomena is to say that damage in the left ventricle (except for the single massive, regional infarcts) tends to begin elsewhere than in the anterior coronary region. In almost four-fifths of the 74 scarred hearts, the earliest scarring was in the right or left circumflex regions: that is, the posterior wall, the basal two-thirds of the lateral wall, and a small part of the posterior septum. Since the incidence of old coronary obstructions was essentially similar for all three regional arteries, other causes must be sought for the above findings.

Differences in the exact severity of obstructive lesions and in their proximity to the origins of the major arteries must have been of great importance. Our method of analyzing the data does not take these into account. We have, further, no way of estimating differences in the speed of development of old coronary obstruction (narrowing or occlusion) although this must be of crucial importance for the development of collateral circulation.[19] Moreover, we could not evaluate the effects on the collateral circulation to any myocardial region of obstruction in the vessels from which the collateral circulation itself must have been coming. It should be borne in mind, however, that stenosing or occlusive coronary lesions might have differed significantly in their myocardial effects not only for the various reasons just mentioned, but because of differences in physiological pressure and flow relationships in the regional muscle perfused by each of the three major arterial trunks. In this connection certain peculiarities of the right coronary region in man are worth considering.

The long right coronary artery's course is mainly over the right ventricle, in the muscle

of which, and in that of the right atrium, all but its most distal branches ramify (see fig. 1). These distal branches supply the posterodiaphragmatic left ventricle in at least 80 per cent of human hearts. Blood flow in the left ventricle's walls during systole must be slight. On the other hand, mural right ventricular pressures are normally low enough to permit continuous perfusion of the muscle even during systole. With a normal right coronary arterial lumen, the pressure drop due to right ventricular systolic perfusion may not seriously prejudice the left ventricular muscle at the distal end of the artery. But any right coronary narrowing by atheroma should put the distal left ventricular muscle at a great disadvantage as compared with the right. Furthermore we have seen two hearts (not in the statistical sample, of course) with posterolateral scars and no coronary narrowings at all.

Collateral blood supply to left ventricular muscle in the distribution of the distal ramifications of the left circumflex coronary artery must come in large part from the right coronary artery. Therefore this muscle also (fig. 1*e*, areas 15 and 23) might have a more precarious blood supply in the presence of even slight right coronary and left circumflex obstruction than would muscle elsewhere in the heart. Unfortunately there are so few instances of monkeys, dogs and other animals having the common human type of long right coronary artery that experimental testing of such hypotheses is difficult.

While small circumflex regional lesions were relatively common, large circumflex regional lesions were not. This fact suggests that the circumflex region can become well supplied with collateral circulation from at least one neighboring region. The circumflex's smaller size may be the entire explanation for this. That the left circumflex artery has no right ventricular distribution may perhaps be another favorable feature. A small amount of left atrial perfusion during systole must of course occur. In any case it appeared that massive circumflex regional damage not only required severe obstruction of both the other major arteries but always involved damage in one or both of these distributions previous to, or at the same time as, that of the circumflex artery.

Finally, to give brief attention to the effects of combined regional ischemia: right-plus-circumflex and anterior-plus-circumflex region combinations together comprised less than 20 per cent of the total for both widespread damage groups. In contrast, either right-plus-anterior combinations or damage in all three regions were found about equally often in four out of every five widespread damage patients. From these phenomena it appears that severe interference with perfusion of both arteries supplying the interventricular grooves is especially likely to be found in hearts with widespread scar or infarction, at least at autopsy.

These arteries constitute the main blood supply to the septum, or intracardiac portion of the left ventricle.[3] An important feature of the normal septum is its profuse intramyocardial vasculature supplied by many penetrating branches from the undersurface of both the "descending" arteries. The septal vascular bed seems to be strategically placed for shunting blood between the anterior and the right (posterior) coronary regions and may constitute an important source of myocardial circulatory flexibility.[1, 10, 23] Once both the main sources of septal circulation are throttled, to the point where at least some muscle is lost in both the anterior and right coronary arterial regions, the patient joins (by definition) one of the "widespread damage" groups. However, the surprising predominance of situations of this type at necropsy—four-fifths of all "widespread damage" hearts—suggests it may be more often lethal than are other combinations.

### 2. *The Necessity of a New Classification*

Our lines of inquiry concerning muscle infarction, scar and localized ischemia seem to neglect other questions which perhaps arise even more commonly in the minds of physicians confronted with "coronary" patients. Has there been a recent coronary thrombosis? is there any old coronary occlusion? and is there reversible coronary insufficiency or spasm? These questions, framed in terms of the

coronary arteries, parallel the lines of inquiry we listed previously. Answers to the questions regarding recent thrombosis and old obstructions have been provided in our data charts. The third question cannot profitably be answered in the present state of our knowledge, since the very existence of coronary spasm is still debated and, in man at least, "coronary insufficiency" is another word for myocardial ischemia. (See part 3 of this Discussion.) We gradually came to realize that descriptive terms derived from coronary lesions or circulatory disturbances were much less valuable for ordering our data or our thinking than we had supposed they would be at the outset of this investigation.

Unlike the situations in experimental animals[13] (see Ischemia), we could not regularly define human heart muscle damage at necropsy in terms of the coronary lesion that must have caused it. The pathologic hallmark of coronary artery disease in man is segmental, epicardial coronary narrowing. *For this there is no time scale and, unless damage is found, no way of estimating circulatory disturbance in the muscle supplied.* Thus, in our sample, even in the exceptional cases wherein only one artery was narrowed, we were unable to say how long severe stenosis had been present. If at necropsy acute thrombosis of an insignificantly narrowed vessel had proved common, we might have thought it roughly analogous to arterial ligation in the dog, but such situations proved comparatively rare.

Thus, in reference to a myocardial lesion in man, we could not say, what has happened is the usual consequence of blocking this size artery, for we did not know whether the artery had been of normal size before it was blocked, or how rapidly any total obstruction had become complete. Indeed, except for coronary embolism or the rare instance, where the surgeon had to ligate a coronary branch in a patient thought to have a normal coronary circulation, it seemed unlikely that we ever could tell what the "expected" muscle sequelae of sudden occlusion of any one coronary vessel in man might be. There seems little hope of distinguishing, by their coronary lesions alone, patients with two or more severely stenosed major arteries; a situation the assessment of which was extremely difficult even in suitably prepared experimental animals.[16]

The coronary lesions thus had a peculiar status in our study. They were essential for evaluating particular muscle lesions;[2] but, once the details of any given ventricular myocardial situation had been established, the coronary lesions became not only inessential but sometimes sources of confusion, in part no doubt, because our methods for estimating collateral circulation were inadequate.

For our purposes, the most important things about the coronary tree in human atherosclerosis were (1) the originally triregional character of the circulation, and (2) the high frequency of stenosing lesions in the larger epicardial trunks, resulting (3) in restrictions of flow (or flow capacity), which almost always differed in degree of severity for one or all three coronary regions. Once the potentially ischemic regions (those at least with a significant coronary narrowing) had been grossly identified at necropsy, muscle lesion evaluation provided the only definitive judgment of actual flow impairment. During life, of course, no direct evidence as to the state of the coronary arteries can be elicited. For purposes of classification and consideration in the clinic and at necropsy, therefore, we felt that arterial lesions could not be given first place.

Our attempts to describe myocardial situations by conventional nomenclature were frustrated by (1) its reliance on anatomic, localizing terms and (2) its inability to deal efficiently with hearts containing multiple lesions. Not more than a third of our hearts contained single, typical "anterior," "posterior" or "lateral" infarcts. They, and the few hearts with more than one lesion but with each infarct or scar having a fairly typical shape, could possibly be described well enough by redefining terms in a prolix fashion; but even this was impossible for the remainder, which comprised over half our sample. For them the ordinary coronary "architecture", on which conventional nomenclature depends, no longer had much meaning. The original coronary distribution patterns seemed to have been

blurred, or erased altogether so far as the shape of the muscle lesions was concerned (see below). Since it was impossible to describe even the anatomic location and distribution of myocardial damage by means of the usual terms, it was hopeless to classify groups of hearts on such a basis. The usual "general" criteria of classification for muscle lesions, "large" or "small," "multiple" or "diffuse," "recent" or "old," failed to bring out important and useful distinctions; indeed, this tended to keep us from paying proper attention to such distinctions. Forced into formulating a new vocabulary, our best approach proved to be classification on the basis of *size* for hearts with single, regional lesions and of *age* for those with multiple or widespread lesions. This avoids the *initial* attempt to describe specific anatomic location.

Of course no classification for coronary disease can dispense with description of anatomic location, but such data were preserved with accuracy in our maps. The frequency charts based on our classification also display certain pertinent pathologic structural relationships in groups of hearts that would not otherwise have been apparent. In the case of particular anatomic damage patterns that were common and consistent enough, verbal reference could easily be achieved by new names.

As in the case of anatomic location our proposed classification permits, but does not directly depend upon, study of the coronary arterial lesions. Indeed it must be remembered that to classify any heart accurately, the ventricular myocardial lesions must first be mapped, a procedure into which the results of both anatomic location and coronary lesion study must always enter.[2, 3]

### 3. *Ischemia*

While our anatomic data have necessarily been confined to only two of three aspects under which the heart muscle in coronary disease must be considered, namely, scars and recent damage, the anatomic backgrounds cannot be properly interpreted without consideration of a third major aspect of the natural history of coronary disease, the threshold and the configuration of localized ischemic areas.

For this discussion we define "ischemia" as a deficiency of myocardial blood supply severe enough to produce evidence of disturbed function: preferably measurable by objective tests but in man also reflected by the anginal syndrome. Thus we can describe myocardial ischemia clinically only as a reversible state reflected by anginal pain or certain electrocardiographic abnormalities, the latter sometimes present only in association with anginal pain or elicited by stress (most often increases of cardiac work or controlled anoxia). The severity and duration of stresses required to elicit evidences of ischemia are rough measurements of its *threshold*. The criterion of reversibility is necessary because irreversible ischemic states, immediately preceding frank infarction, seem still to be inaccessible to study or in vivo definition.

In experimental animals we can define and measure localized ischemia with some precision. Upon the establishment of a sufficiently severe segmental coronary narrowing, there ensues a fall in local oxygen tension, disturbed local repolarization, increased muscle irritability, and diminished strength of muscle contraction.[13, 14] These signs of localized ischemia follow narrowing of lesser severity if accompanied by reduced coronary perfusion pressure,[21] increased blood viscosity, anoxic stresses,[17] or other disturbances of the general coronary circulation sufficient to put muscle with restricted blood flow at a disadvantage. *Localized myocardial ischemia* is then a consequence of either diminished local blood flow or inability to respond to a call for hyperemia *in a part* (or parts) *of the ventricular muscle when the remainder has a normal or relatively normal blood supply.*

It is important to differentiate *localized* ischemia, with its low threshold situations and easily-upset balances, from what might be called diffuse or "physiologic" ischemia. Extremely severe dynamic or anoxic stresses may damage the heart muscle even in the absence of stenosing arterial disease. In animals subjected to violent exertion (especially when anemic), acute necrosis has been demonstrated

in the left ventricle and septum.[11] It has been described in certain patients with pulmonary embolism[12] and carbon monoxide poisoning[22] although in most instances coronary disease had either been demonstrated or had not been excluded with certainty. These situations, however, are characterized by *high* thresholds. It is quite difficult to produce myocardial necrosis this way in animals with "normal" coronary arteries. Anatomic changes are uncommon, difficult to interpret, and very limited in extent when they do occur: at most, a few scattered foci of necrosis in trabeculae near the left ventricular cavity.

No myocardial changes precipitated by defective blood supply can be truly "diffuse". It is well known that the inner layers of the systemic ventricle—the left ventricular walls and their intracardiac continuation in the septum—constitute a myocardial point of least resistance. Differences in intramural pressure and a remoteness from their blood sources must cause these inner layers of the systemic ventricle to be at a disadvantage, not great perhaps but ineluctable if sufficient stress be applied. At present such a disadvantage is difficult to demonstrate and almost impossible to measure. The ordinary experimental or clinical ischemia indices, so far as we know, depend on there being considerable amounts of relatively "normal" left ventricular muscle, which can keep a circulation going and permit a less advantageously supplied portion of the heart to be forced into mechanical failure by the intraventricular pressures generated by the "normal" muscle. Only under these conditions can the disturbances in muscle contraction and repolarization which we must depend on for early experimental recognition of ischemia be expected to develop.

In man, well-documented cases of muscle necrosis without coronary stenosis are rare, except when aortic valve disease is present. Aortic stenosis and insufficiency provide transitional situations that may produce medium or low threshold ischemia with relative evenness of coronary flow deficiency throughout the ventricles. While in living patients with aortic valve lesions it is frequently impossible to exclude inequalities of coronary lumen patency due to ostial (syphilitic) obstruction or segmental atheroma, an appreciable number of patients with aortic valvular disease and clearcut histories of anginal type pain come to necropsy with entirely patent coronary vessels and yet with recent subendocardial left ventricular necrosis.

Thus there is need for terminological distinction among at least three ischemic situations: (1) diffuse "physiologic," high-threshold ischemia; (2) diffuse "aortic," medium-threshold ischemia; and (3) the "*localized*," subventricular, low-threshold ischemias that are limited almost completely to coronary disease. Such distinction has been made difficult because it is now customary to refer indiscriminately to any of the localized or generalized, low- or high-threshold types of ischemia as "coronary insufficiency", thus emptying the term of useful significance. If it is to retain any clear-cut meaning at all, "coronary insufficiency" should be reserved for the "aortic" type of generalized ischemia, or experimental analogues of it.[18] As it is now, the term is actually an obstacle to critical consideration of myocardial ischemic situations.

Indeed, it is not enough to designate three types of myocardial ischemia. Our studies suggest that at least two varieties of *localized* ischemia must be borne in mind, *regional* ischemia and *widespread* ischemia. The latter is a type of localized circulatory inadequacy affecting *more than one coronary region*. It resembles the "physiologic" and "aortic" varieties of generalized ischemia in damaging especially the subendocardial layers of the left ventricle and septum, but differs from "physiologic" ischemia in having a *low* threshold. It is a step *beyond* regional ischemia into a still more severe distortion of the coronary perfusion "architecture."

In our sample of human coronary disease, it was not uncommon to find widespread acute infarction affecting parts of the distributions of two major regional arteries, *even in the absence of acute coronary thrombosis*. In 40 per cent of the "widespread acute infarction"

hearts (group IV), no recent coronary thrombus was demonstrated. Furthermore, single acute thrombi were sometimes associated with infarcts which, while they involved only a portion of the original distribution of the affected artery, at the same time, extended well beyond that region.

Such phenomena must signify advanced distortion of the original coronary perfusion "architecture." Progressive coronary obstruction presumably had caused collateral circulation to become one of the major factors conditioning the pattern of perfusion, not merely in one region, but throughout most of the ventricular muscle. While epicardial vessels doubless contribute something, it is clear from injection studies of hearts, and consideration of the rather strict limitation of atheroma to epicardial arterial trunks, that intramyocardial vessels must be the chief conduits of collateral blood flow.[10, 22] Such flow can be expected to blur or change completely all the original patterns of epicardial arterial distribution.

The response to stress of a heart containing a low-threshold *widespread* ischemic area might be expected to differ considerably from that of a heart whose low-threshold muscle is restricted to not more than a single coronary region. The difference would not have to be a simple quantitative one, proportioned to greater restriction of total coronary blood flow. Any failure of muscle contraction consequent to ischemia of crucial severity would, in a regionally ischemic heart, consist of a localized systolic "bulge" such as can readily be reproduced in the experimental animal. In a widespread ischemic heart the mechanics of systole would be deranged in a much more complex way because of failure of muscle contraction, especially of the inner layers, throughout most of the left ventricle. With prolonged regional ischemia, the common consequence is infarction and ultimate scar formation (predominantly subendocardial).[15] With widespread ischemia, the consequences are almost unknown, though a fatality is not necessarily to be expected. Clearly, however, the more widespread the ischemic zone and the greater the amount of scarring already present in any heart, the less it can "afford to lose" ischemic muscle by frank infarction.

Analogous ischemic situations have been produced in suitably prepared experimental animals. If we obstruct one coronary artery, ischemia is demonstrated regularly in the distribution of this artery but not in those of the others. If the left anterior descending *and* the circumflex are *gradually* obstructed without demonstrable ischemia in the distribution of either, and weeks later, a circulatory stress previously harmless to the animal is then added, evidences have been produced of ischemia followed by sudden death or, after a sufficient period of survival, massive acute necrosis in the distribution of both arteries.[9]

In man a simple distinction between widespread and regional ischemia on the basis of coronary lesions alone has not been possible. Multiple severe narrowings were too common, and the efficacy of collateral circulation too difficult, to estimate. However, it seems fair to assume that the occurrence of widespread muscle damage in coronary disease patients provides the soundest basis for inferring the presence of actual or potential widespread ischemia.

Widespread damage was present in more than half our sample, but our data show it must have developed in more ways than one. Many patients suffered recurrent episodes of muscle loss, resulting characteristically in widespread subendocardial scarring. Presumably there must have been residual or potential ischemia at many scar sites. Late (usually terminal) acute infarction episodes under such circumstances often consisted of spotty acute damage near one or more of the old scars, with or without a distinct larger area of infarction. The mass of the recently damaged muscle might or might not have been large but its comparative importance doubtless increased in relation to the amount of ventricular muscle that had already been lost. This general type of behavior was represented by our group III patients. In contrast were the widespread infarction patients of group IV who lost little or no muscle until their potentially ischemic

areas were revealed, wholly or in part, by a terminal infarction.

It was also our opinion that in the same hearts there might well exist localized ischemic zones that differed slightly in their thresholds. One zone might be made ischemic by an exertional circulatory stress or the interference with flow through small vessels that is supposed to follow a fatty meal.[20] A second zone, with a higher threshold, might become involved only when the blood pressure fell severely as a consequence of failure of the first area to contract. Thus a downward spiral of disturbed myocardial function would be initiated. Certainly in some of our widespread infarction hearts, portions of the terminal acute infarct differed somewhat in histologic age. Such phenomena were almost never explainable on the basis of extension of a thrombus or the presence of more than one clot.

The presence of regional or widespread ischemic areas, actual or potential, cannot be left out of consideration either for evaluation of living patients or in clinicopathological retrospect. While we cannot at present quantify ischemia or even make a direct demonstration of its full extent at necropsy, it is possible to make a crude estimate from (1) the original anatomic distribution of the coronary branch or branches most severely or recently obstructed, (2) the degree of distortion of coronary perfusion "architecture" as reflected in the shape of old and new muscle lesions, and (3) clinical data as to threshold and frequency of anginal pain. (Details of our methods of estimation will be given in part V of this study.[5])

Patients with large and small regional areas of potential ischemia might be expected to differ considerably in their circulatory physiology, both from each other and from patients with widespread ischemic areas. The differences may be further altered by previous myocardial scarring. Indeed, it would seem that the size and threshold of its ischemic area (or areas) might be the most prognostically significant feature of any heart that is the seat of obstructive coronary disease. Whether or not there has been muscle destruction in any area is an important consideration but it is water over the dam, whereas ischemia is pregnant for the future.

4. *Answers to the Basic Lines of Inquiry Provided by the Proposed Classification*

In summary, we return to the questions that must be asked about any living patient having known or suspected coronary disease.

(1) *Is there a low-threshold, localized ischemic area?* If so, is its distribution regional or widespread?

(2) *How much muscle has been lost and replaced by scar?* Does the scar itself have a regional or widespread distribution? In addition to the lowered threshold for ischemia in the immediate vicinity of any scar, is there also an ischemic area involving any considerable part of the residual, anatomically "normal" muscle?

(3) *Is there acute infarction?* If so, is it regional or widespread and large or small with respect to the viable muscle? Does it involve most of the patient's previously potentially ischemic area or has only part of this become infarcted, so that considerable low threshold muscle is hanging in the balance? How large a scar will the infarct leave if it heals? Can the patient "afford" to lose his low-threshold ischemic areas?

These questions are restated in what might be called the physiologist's order, starting with the initial types of disturbance and with the more fundamental situations. Therefore ischemia must be the central theme. It has to be considered first, and then reconsidered with each of the essentially secondary lines of inquiry regarding old and new damage. Our previous order of questions (in the introductory paragraphs) may be preferable for clinical and pathologic purposes, since it proceeds from phenomena relatively well-diagnosed during life and having important therapeutic indications (acute damage), to those sometimes ascertainable only by the autopsy (scars), to phenomena whose exact status can only be inferred (ischemia). However, regardless of the order, or of the efficiency of the available

TABLE 2.—*Features of Types of Myocardial Ischemia Discussed, Showing Their Relation to the Classification Derived from the Muscle Lesions*

| Basic Types | "Generalized" | | Localized (Subventricular) | | | |
|---|---|---|---|---|---|---|
| Subtypes | "Physiologic" | "Aortic" (Stenosis or insuff.) | Regional | | Widespread | |
| Threshold | High | Medium or Low | Low | | Low or very low | |
| Coronary perfusion "architecture" | Normal | Normal. Perfusion pressures inadequate | Locally distorted with blood supply to one region (or portion) inadequate. Usual regional distributions fairly well maintained | | Severely distorted with blood supply to at least two regions inadequate. Collateral circulation blurs or obliterates usual regional distributions | |
| Precipitating causes | Anemia plus severe stress or anoxia (animals)<br>Carbon monoxide, pulmonary embolism (?) (man) | Stresses producing anginal pain<br>Hypotension<br>Anoxia<br>Anemia | Reversible: stresses producing anginal pain<br>Irreversible: coronary thrombosis (at narrowed site) rarely embolism | | Reversible: stress may be very slight: emotion, recumbency, fatty meals<br>Irreversible: usually coronary thrombosis, sometimes acute anemia and hypotension without thrombosis | |
| | | | Group I | Group II | Group III | Group IV |
| Early anatomic consequences | Spotty necrosis: inner layers of left ventricle | Subendocardial left ventricular necrosis (if severe) | Subendocardial regional infarction: new, or in a scarred region | Transmural regional infarction | One of multiple, successive infarcts leaving subendocardial scars | Acute, wide spread subendocardial infarction |
| Late anatomic consequences | None known | Fine subendocardial scarring. Degenerative myocardial changes | Subendocardial, regional or subregional scar | Transmural, regional scar | Widespread scar sheets or multiple scars | No survivals in our sample. May cause some widespread scar sheets |

means for obtaining the answers, we believe that these three inquiries are of fundamental importance. *Questions of this sort must be answered, or at least have attention drawn to them, by any classification for coronary disease that is to have permanent usefulness for clinicians or for investigators.*

Answers to the three lines of inquiry, summarized in table 2, are now briefly reviewed.

(1) *Is there a localized ischemic area?* Our group I patients did not appear to have had ischemia except in the vicinity of their small, localized scars, and thus in a part of, at most, one coronary region; at least, acute necrosis was never demonstrated elsewhere. Thus we conclude tentatively that they had small, regional ischemic areas. Group II patients did not show evidence of ischemia outside the single, large regional lesion or potential area of infarction characteristic of the group. Group III patients commonly presented evidences of having had multiregional or widespread ischemia, its importance presumably being the greater the less was the amount of unscarred

muscle in any heart. They might also have had multiple but successive ischemic areas with or without differences of threshold between potentially ischemic scar sites and muscle not yet anatomically disturbed. These pictures eventually might become very complex. Group IV patients appeared to have had widespread ischemic areas involving the inner layers of anatomically "normal" muscle and jeopardizing much of the myocardium, their configuration being at least revealed, at least in part, by terminal infarction.

(2) *How much muscle has been replaced by scar?* Only group III patients invariably had ventricular scars, but small regional healed lesions were commonly present in groups I and IV, almost all being subendocardial. Half of group II had a single transmural scar, presumably the residuum of a large localized transmural infarct. Thus the anatomic muscle reserve had been greatly reduced in group III and in some members of group II (that is, in 42 per cent of our series), though in different ways.

(3) *Is there acute infarction?* If acute infarction was present, group I patients had a "small" lesion that was associated with a low mortality; group II patients had a compact but large through-and-through lesion that very frequently was lethal; group III patients might have almost any type of infarction superimposed on extensive scarring of various degrees; while group IV patients had widespread, subendocardial damage, which in this series was uniformly associated with a fatality. Group IV patients often developed one penetrant area of transmural infarction later in the terminal episode of acute damage. In general their behavior suggested that not all of their potentially ischemic zone was infarcted simultaneously.

Without classification by total ventricular situation the multifarious data of our sample could not have been presented except in the form of a series of individual case reports. We have mentioned certain clinicopathologic features that seem characteristic of patients in each group and that provide ground for thinking the basic situations may some day be better recognized during life. Whether or not our groups have direct clinical relevance, in that they will make it possible to categorize living patients with diagnostic advantage, will be discussed, in connection with electrocardiograms, in part IV.[4] However, their *indirect* relevance to the understanding of obstructive coronary disease in man seems unquestionable, provided the three lines of inquiry we have defined above are relevant. Indeed, the basic groups, as defined in words or symbolized in schemata, simply epitomize common and distinct combinations of answers to these questions.

If the answers, though differing widely, are yet characteristic for each group, then the groups themselves must be borne in mind whenever the physician looks back upon the course of his patients from the eminence of the necropsy and tries to evaluate methods of clinical study or treatment. Indeed, only after the three proposed lines of inquiry have been followed through, is it possible to make a fair estimate of the most important physiologic feature of any patient's heart: the strength, size and circulatory reserve of its residual muscle.

One of the many sources of confusion in clinical studies of coronary disease is the difficulty of evaluating ventricular hypertrophy, chamber dilatation and their end results in the form of congestive failure. Coronary disease is the great diagnostic category where "cured" hypertensives abound. In our series we could often document pronounced falls of blood pressure (to normal or much lower figures) which might be transient or permanent. Often, however, we did not know whether high or higher blood pressures preceded any "normal" figures obtained. At necropsy ventricular hypertrophy, best estimated by weighing the muscle, is a fair value only if little or none of it has been replaced by scar. Furthermore, we could not be sure whether muscle appearing under the microscope to be hypertrophic, a difficult and unsatisfactory method at best, had become so in response to a previous systemic hypertension or to the increased work of ventricular emptying. For example, myocardial scarring, with stiffening of the heart walls or a frankly bulging "aneurysm", must

increase the work of the residual muscle not only by reducing the original number of muscle fibers but also by making mechanical systole laborious and inefficient. In the present study we have not yet evaluated heart weights and data concerning present and previous hypertension. The criteria for definition of our groups are independent of those factors.

Thus, our three lines of inquiry are really preliminary approaches to even more fundamental problems. They are designed to ascertain the background on which localized ischemia, if it has a low enough threshold to be recognized by available methods of clinical study, may occur; and to group together patients with similar anatomic backgrounds and low-threshold localized ischemic areas of the regional as contrasted with the widespread varieties. The first task is the precise definition of groups of patients or animals similar in amounts of available functioning myocardium, in degrees of past or present hypertensive stress, and in mechanical handicaps such as subendocardial scar sheets or transmural scar "aneurysms." Only then may we hope to study and understand the behavior of the new physiologic world of the "intramyocardial" circulation that collateral, small-caliber vessels have created; and in which the familiar patterns of physiologic behavior or pharmacologic responses may be greatly altered. In such an approach there would seem to be important advantages for the definitive evaluation of therapeutic agents and the clinical or experimental investigation of myocardial dynamics and electrical phenomena in coronary disease.

## Summary and Conclusions

(1) From 250 autopsied cases in which the ventricular myocardium and the coronary vessels were carefully explored, 100 cases were selected on the basis of (1) a severe narrowing of at least one major coronary vessel, and (2) a recent electrocardiogram.

(2) The age, thickness and extent of the myocardial infarcts and scars were plotted for each case on a myocardial map. A record was also made of the presence of recent thrombosis, old narrowing or occlusion in the three main coronary arteries: the left anterior descending, the left circumflex, and the right. In addition, the original anatomical configuration of these three main coronary regions was estimated from the epicardial arterial system.

(3) The myocardial map was subdivided into 24 numbered areas, some of which were shown by means of a review of the coronary artery distribution in all of the cases, to lie almost invariably within the distribution of one and only one of each of the three coronary vessels. These "central" areas were distinguished from peripheral areas in which the coronary artery of supply was either occasionally or usually uncertain ("probable" and "uncertain" areas). A chart was then constructed with the 24 areas arranged in a simple horizontal row, so that the central and probable areas of each region were kept in groups, separated from each other by contiguous uncertain areas. By the use of appropriate symbols, the character and amount of myocardial damage for each case could be represented along a single line, which made it further possible to demonstrate common relationships in groups of cases.

(4) With respect to the coronary arteries, it was found that in 87 per cent of the cases *more than one vessel* was severely obstructed. However, in many cases severe narrowing or old occlusion were not accompanied by evidence of scar in the region of distribution. The incidence of old occlusion or narrowing was nearly the same for all three coronary arteries: about 85 per cent. Recent thrombi were found with about one-third the frequency of old lesions, the left circumflex artery being involved less often than the other two.

(5) Concerning the configuration of myocardial damage, it was found that in 42 cases the damage, old or recent, was confined to the distribution area of one coronary artery. This type of damage was called *regional*, in contrast to the *widespread* damage found in 56 other cases (two or three coronary regions involved). In two cases there was no damage. The cases of regional damage divided themselves into two approximately equal groups on the basis of the size of the lesion: group I, *small regional lesions*; and group II, *large*

*regional lesions.* The hearts with widespread damage also fell into two groups: group III, *widespread scar*, 36 cases with healed scar in the central areas of two or more regions; and group IV, *widespread acute infarction*, 20 cases with this type of lesion in two or more regions, and little or no scar.

(6) This method of classification was simple, and it proved relatively free of ambiguity. It made possible the consideration and rapid comparison of total ventricular myocardial situations for groups of hearts in a way that was not possible with classification by anatomic location or coronary artery lesions.

(7) One important relationship brought out by this method of analysis was the peculiarly high or low incidence of certain types and combinations of muscle damage, despite the rather even distribution of coronary artery obstructions. Isolated small muscle lesions were frequent in the posterior and lateral regions of the left ventricle, but were never found in the anterior region. Large isolated anterior lesions were occasionally seen, but small anterior lesions, though common, were always associated with other, usually older, lesions in other regions of the heart. Muscle damage in the left ventricle tended to begin in regions other than the anterior.

(8) The myocardial lesions appeared to reflect two degrees of disturbance of the coronary perfusion "architecture:" (1) preservation of the usual anatomic arterial distributions even in badly damaged hearts, as in the single, localized lesions of groups I and II, and (2) blurring or distortion of the perfusion patterns because of multiple epicardial artery obstructions and well-developed intramyocardial collateral circulation. This latter type of ventricular situation might develop gradually, as in the multiregional scars of group III, or be revealed suddenly by widespread acute infarction, as in group IV.

(9) Although the postmortem classification was not based on the estimated extent and threshold of localized ischemic areas, scrutiny of coronary lesions and clinical phenomena in relation to muscle damage configurations suggested characteristic and different areas of actual or potential ischemia during life for each of the groups. A clinical classification framework based on localized ischemia was outlined and related to the postmortem groups.

(10) The proposed nomenclature and classification have, we believe, set in order a complex body of data that could not otherwise have been described except as a series of separate case reports. The present report is to serve as an introduction and as an atlas for subsequent papers dealing with the electrocardiographic and pathologic findings.


### Summario in Interlingua

Esseva elaborate methodos que permitte le studio detaliate del lesiones resultante de morbo coronari e le exacte reconstruction del forma de omne lesiones del musculo ventricular. Iste methodos esseva applicate a 100 consecutive patientes electrocardiographate qui habeva al minus un sever constriction coronari. Le typos de lesiones observate requireva un reclassification in quatro categorias. Iste procedimento resulta in conclusiones in re le evolution de damnos muscular e le relation inter obstructiones arterial e le distribution del damnos muscular; illo etiam demonstra le signification de ischemia. Previemente isto non esseva possibile. Le valor del nove classification pro ojectivos electrocardiographic va esser discutite in un section futur de iste reporto.


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# The Neurogenic Component in Hypertension

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The magnitude of the blood pressure falls, in the horizontal posture, following intravenous hexamethonium, shows that an important part of the blood pressure elevation is neurogenically maintained in essential hypertension. When the blood pressure is first raised by angiotonin or by other pressor agents, the subsequent response to hexamethonium is much reduced. Similar responses are observed in normotensive and hypertensive subjects. This is due to the reaction of the regulating centers which compensate for the effect of the pressor agent by reducing the neurogenic component. The resulting decrease in the neurogenically maintained fraction of the blood pressure diminishes the response to hexamethonium. It is suggested that, in the course of time, long exposure to pressor stimuli induces the vasomotor centers to exercise their regulating function at a higher than normal level.

THE PHARMACOLOGY of hexamethonium salts was first studied by Paton and Zaimis.[1] These workers reported that the substance acted predominantly at the autonomic ganglia, and were able to show that small concentrations of hexamethonium caused blocking of the ganglia. It was soon evident from clinical studies that the predominant action of hexamethonium in man is also to produce autonomic ganglionic block. Arnold and Rosenheim[2] demonstrated that the substance caused a sharp fall of blood pressure and that postural hypotension occurred. Peripheral vasodilatation occurs, being greater in the legs than in the arms.[3] The fall in blood pressure appears to depend on the interference by the drug with the capacity of the sympathetic nervous system to perform its normal circulatory reflex functions; thus, in the erect posture, the blood pressure falls because of the absence of sympathetic vasoconstriction, and a similar additional fall of blood pressure usually follows meals.[4]

Reports on the effects of the drug on the cardiac output in man have been conflicting. Gilmore and associates,[5] Freis and his coworkers,[6] and Rakita and Sancetta[7] reported that the cardiac output was usually little changed following the administration of hexamethonium and that the fall in blood pressure was due to a fall in the peripheral resistance. In a later report Freis and coworkers[8] have reported that the cardiac output remains unchanged or rises in patients with malignant hypertension or heart failure, but in those with benign essential hypertension the cardiac output usually falls. Studies on the effect of the drug on cardiac output in dogs have likewise been conflicting, Moyer and his colleagues[9] finding no fall in cardiac output whilst Crumpton and associates[10] report that the fall of blood pressure induced by hexamethonium is accompanied by significant decrease in the cardiac output, with an increase in the calculated total peripheral resistance. All workers are agreed, however, that when the cardiac output falls, it does so as a result of pooling of blood in the extremities which follows the peripheral vasodilating action.

Arnold and Rosenheim[2] showed that the fall of blood pressure after hexamethonium was usually larger in the hypertensive than in the normotensive subject; Conway[11] and Barnett and Fraser[12] have reached similar conclusions. It is now generally conceded that many hypertensive subjects have greater blood pressure falls than normotensives. This might seem to imply that the neurogenic component in hypertension is greater than in health, since the vasodilatation which causes the fall in blood pressure is predominantly due to the block of the sympathetic ganglia. Such a view may be an over-simplification, however, for the view has been expressed that, even if the

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blood vessels were constricted primarily by the action of a chemical pressor substance, the effect of nervous stimulation would be thereby enhanced. If such an enhancement of the effects of nervous stimulation occurred, an exaggeration of the blood pressure fall would result from the removal of normal autonomic constrictor impulses. If the effect of the normal neurogenic component became increased in this manner as the result of the elevation of the blood pressure, it would seem likely that if the blood vessels were further constricted as a result of the action of a chemical pressor substance, the effect of the neurogenic component would be further enhanced.

It was decided to test this hypothesis experimentally in man by measuring the depressor action of hexamethonium in hypertensives and normotensives under standard conditions, and again after the artificial elevation of the blood pressure by various chemical pressor substances. In the present study we have observed the depressor action of hexamethonium under these conditions using angiotonin, noradrenaline or s-methyl isothiourea to elevate the blood pressure.

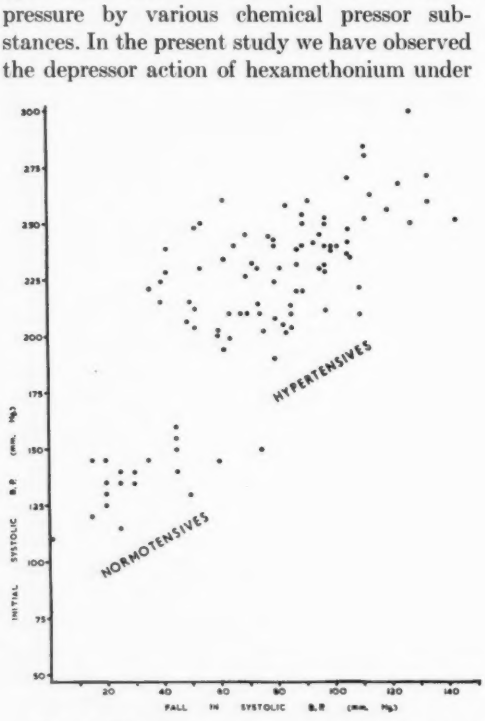


FIG. 1. The relation between the initial casual systolic blood pressure and the fall in systolic blood pressure (horizontal posture) following a "maximal" intravenous dose of hexamethonium. The results include normotensives and hypertensives.

## METHODS

Blood pressures were recorded by the auscultatory method in accordance with the recommendations of the joint Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the British Cardiac Society, 1939. Observations were made both with the subjects recumbent and on a tilting table with the feet tilted down to 60 degrees. A needle was introduced into the median basilic vein and a slow infusion of 5 per cent glucose given. Intravenous injections were made by means of a three-way tap so that injections could be given without the patient's knowledge.

For testing the depressor action of hexamethonium in the recumbent position, the initial dose was usually 25 mg.; subsequent doses of 15 mg. were given at two-minute intervals until two successive doses had produced no further fall in the blood pressure. When the subject was on the tilting table at 60 degrees the initial dose was 15 mg. and increments of 5 mg. were given at intervals of three or four minutes until faintness was noticed or until the systolic blood pressure fell below 70 mm. Hg.

The responses obtained by the methods described above were compared in some patients with the responses to similar doses during the administration of the humoral pressor substances noradrenaline, angiotonin or s-methyl *iso*-thiourea. In this test 5 units of angiotonin were given at two-minute intervals and the blood pressure was recorded at half-minute intervals. When the blood pressure had become stable, the dose of hexamethonium prevously effective was again given intravenously. The injections of angiotonin at two-minute intervals were continued until such time as the period of maximal action of the hexamethonium, as judged from the previous test, might have been expected. When s-methyl *iso*-thiourea was used, the dose was 50 mg. at two-minute intervals. When noradrenaline was used it was administered by an intravenous drip of 5 per cent glucose containing 2 micrograms of noradrenaline per milliliter. The rate of the drip was adjusted to give a suitable rise of blood pressure.

## RESULTS

### (a) *Depressor Effect of Hexamethonium in Recumbent Hypertensive Patients*

Observations were made in 80 subjects with hypertension of various clinical types. The mean systolic blood pressure for the group was 233 mm. Hg (S. D. ± 23) and the mean diastolic pressure was 133 mm. Hg (S. D. ± 15). The mean fall in systolic pressure was 85 mm.

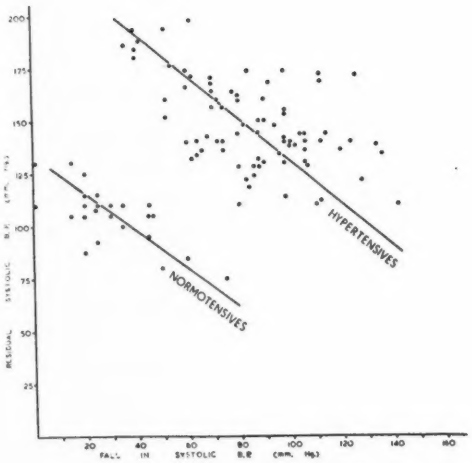


FIG. 2. The relation between the "floor" or "residual" blood pressure after administration of a "maximal" intravenous dose of hexamethonium and the extent to which the blood pressure is reduced by hexamethonium. It is seen that both in normotensives and in hypertensives the patients with higher residual pressures tend to have the smaller blood pressure falls.

Hg (S. D. ± 24) and the mean fall in diastolic pressure was 37 mm. Hg (S. D. ± 16.5). The positive relationship between the size of the fall in systolic blood pressure and the initial systolic level is shown in figure 1. The coefficient of correlation between these two measurements was 0.557, which is highly significant ($p < .001$).

The extent of the blood pressure fall could not be predicted on clinical grounds in any individual patient. There was no correlation between the grading of the fundi and the sensitivity to hexamethonium, and in particular patients with malignant hypertension seemed to exhibit average sensitivity to the drug. There was no important correlation between the age of the subject and the extent of the blood pressure fall. With numerous exceptions there was a slight tendency for the more elderly subjects to have larger falls of blood pressure.

The level to which the blood pressure fell after hexamethonium also varied widely, the mean systolic level being 148 mm. Hg (S. D. ± 21.5) and the mean diastolic level being 95 mm. Hg (S. D. ± 18). Figure 2 shows that there is an inverse relationship between the level of the blood pressure after hexamethonium (i.e. residual or floor pressure) and the extent of the blood pressure fall, those patients who had large falls of blood pressure having a low level after hexamethonium whilst those who had a high level after hexamethonium had only small falls of blood pressure. The coefficient of correlation between these two measurements was $-0.521$ ($p < .001$).

(b) *Depressor Effect of Hexamethonium in Recumbent Normotensive Subjects*

Observations were made in 22 subjects with normal blood pressures. The mean initial systolic pressure was 137 mm. Hg (S. D. ± 12) and the mean initial diastolic blood pressure was 82 mm. Hg (S. D. ± 7). The falls of blood

TABLE 1.—*Falls of Blood Pressure Induced in Recumbent Hypertensives by Intravenous Hexamethonium, under Standard Conditions and During the Infusion of Angiotonin (5 Units Every 2 Minutes)*

| No. | Hexamethonium alone | | | Hexamethonium after angiotonin | | | Result |
|---|---|---|---|---|---|---|---|
| | B.P. before | B.P. after | Fall | B.P. before | B.P. after | Fall | |
| 1 | 210/130 | 165/100 | 45/30 | 210/130 | 200/125 | 10/5 | Fall less |
| 2 | 220/110 | 140/70 | 80/40 | 250/120 | 190/110 | 60/10 | Fall less |
| 3 | 200/110 | 180/90 | 20/20 | 260/160 | 260/160 | 0/0 | Fall less |
| 4 | 170/110 | 145/80 | 25/30 | 180/120 | 180/120 | 0/0 | Fall less |
| 5 | 170/90 | 135/70 | 35/20 | 195/105 | 175/110 | 20/0 | Fall less |
| 6 | 255/130 | 120/70 | 135/60 | 285/155 | 240/140 | 45/15 | Fall less |
| 7 | 280/130 | 220/130 | 60/0 | 300/170 | 295/170 | 5/0 | Fall less |
| 8 | 260/120 | 160/80 | 100/40 | 280/130 | 220/110 | 60/20 | Fall less |
| 9 | 200/120 | 155/100 | 45/20 | 235/140 | 215/140 | 20/0 | Fall less |
| 10 | 220/100 | 160/90 | 60/10 | 265/120 | 180/110 | 75/10 | Fall greater |
| 11 | 220/120 | 180/100 | 40/20 | 270/135 | 255/135 | 15/0 | Fall less |

TABLE 2.—*Falls of Blood Pressure Induced in Recumbent Hypertensives by Intravenous Hexamethonium, under Standard Conditions and during the Infusion of Noradrenaline (2 μg. per ml.)*

| No. | Hexamethonium alone | | | Hexamethonium after noradrenaline | | |
|---|---|---|---|---|---|---|
| | B.P. before | B.P. after | Fall | B.P. before | B.P. after | Fall |
| 1 | 250/140 | 160/100 | 90/40 | 265/150 | 250/150 | 15/0 |
| 2 | 220/120 | 120/85 | 100/35 | 220/120 | 170/100 | 50/20 |
| 3 | 200/120 | 130/90 | 70/30 | 225/130 | 200/130 | 25/0 |
| 4 | 195/120 | 165/110 | 30/10 | 250/140 | 250/140 | 0/0 |
| 5 | 230/130 | 145/90 | 85/40 | 270/130 | 220/120 | 50/10 |
| 6 | 260/140 | 235/140 | 25/0 | 300/170 | 295/170 | 5/0 |
| 7 | 190/95 | 135/85 | 55/10 | 210/115 | 210/115 | 0/0 |
| 8 | 240/140 | 180/115 | 60/25 | 270/165 | 270/155 | 0/10 |

pressure were much smaller in the normotensive subjects than in the hypertensive group, the mean fall in systolic pressure being 31 mm. Hg (S. D. ± 18) and the mean fall in diastolic pressure 15 mm. Hg (S. D. ± 11). As in the hypertensive group, there was a correlation between the size of the initial pressure and the fall of blood pressure, the coefficient of correlation being .618 ($p < .001$). In contrast to the results in the hypertensive patients there was a close correlation between the ages of the patients and the extent of the blood pressure fall, but since the elderly subjects tended to have rather higher casual pressures and lower residual pressures, both of which seemed to be associated with larger blood pressure falls, it is not possible to determine to which of these factors the increased fall in blood pressure can be related.

As in the hypertensives, there was an inverse relationship between the height of the residual blood pressure and the extent of the fall in blood pressure. The mean systolic level after hexamethonium was 106 mm. Hg (S. D. ± 14)

TABLE 3.—*Falls of Blood Pressure Induced in Hypertensives while Tilted to 60 Degrees Feet Down by Intravenous Hexamethonium under Standard Conditions and During the Infusion of Angiotonin*

| No. | Hexamethonium | | | Hexamethonium after angiotonin | | | Results |
|---|---|---|---|---|---|---|---|
| | B.P. before | B.P. after | Fall | B.P. before | B.P. after | Fall | |
| 1 | 180/120 | 110/90 | 70/30 | 160/110 | 160/110 | 0/0 | Fall less |
| 2 | 230/160 | 145/95 | 85/65 | 255/140 | 240/140 | 15/0 | Fall less |
| 3 | 235/130 | 115/90 | 120/40 | 235/140 | 190/130 | 45/0 | Fall less |
| 4 | 175/85 | 120/70 | 55/15 | 195/100 | 155/90 | 40/10 | Fall slightly less |
| 5 | 225/140 | 105/85 | 120/55 | 170/120 | 120/90 | 50/30 | Fall less (? significant) |
| 6 | 230/140 | 145/100 | 85/40 | 250/150 | 200/140 | 50/10 | Fall less |
| 7 | 160/120 | 95/70 | 65/50 | 175/115 | 115/80 | 60/35 | Fall slightly less |
| 8 | 230/150 | 140/105 | 90/45 | 225/180 | 215/165 | 10/15 | Fall less |
| 9 | 145/105 | 100/80 | 45/25 | 240/170 | 225/150 | 15/20 | Fall less |
| 10 | 145/100 | 85/70 | 60/30 | 225/160 | 190/150 | 35/10 | Fall less |
| 11 | 244/156 | 165/120 | 80/35 | 265/170 | 250/160 | 15/10 | Fall less |
| 12 | 240/140 | 170/100 | 70/40 | 275/150 | 250/130 | 25/20 | Fall less |

TABLE 4.—*Falls of Blood Pressure Induced in Hypertensives while Tilted to 60 Degrees Feet Down by Intravenous Hexamethonium, under Standard Conditions or During the Infusion of S-methyl Iso-Thiourea*

| No. | Hexamethonium alone | | | Hexamethonium after s-methyl *iso*-thiourea | | | Result |
|---|---|---|---|---|---|---|---|
| | B.P. before | B.P. after | Fall | B.P. before | B.P. after | Fall | |
| 1 | 230/160 | 145/95 | 85/65 | 290/160 | 260/150 | 30/10 | Fall less |
| 2 | 235/130 | 115/90 | 120/40 | 190/130 | 150/100 | 40/30 | Fall less |
| 3 | 175/85 | 120/70 | 55/15 | 225/130 | 175/100 | 50/30 | Fall slightly greater |
| 4 | 180/190 | 110/70 | 70/20 | 185/120 | 150/90 | 35/30 | Fall slightly less |
| 5 | 220/120 | 160/100 | 60/20 | 220/140 | 220/140 | 0/0 | Fall less |
| 6 | 230/140 | 145/100 | 85/40 | 275/180 | 240/160 | 35/20 | Fall less |
| 7 | 230/150 | 140/105 | 90/45 | 260/180 | 245/170 | 15/10 | Fall less |
| 8 | 215/150 | 85/65 | 130/85 | 270/150 | 210/140 | 60/10 | Fall less |

TABLE 5.—*Falls of Blood Pressure Induced in Recumbent Normotensives by Intravenous Hexamethonium under Standard Conditions and During the Infusion of Angiotonin (5 Units every 2 Minutes)*

| No. | Hexamethonium alone | | | Hexamethonium after angiotonin | | | Result |
|---|---|---|---|---|---|---|---|
| | B.P. Before | B.P. After | Fall | B.P. before | B.P. after | Fall | |
| 1 | 130/80 | 110/80 | 20/0 | 140/90 | 120/90 | 20/0 | Same |
| 2 | 145/90 | 130/85 | 15/5 | 160/110 | 155/110 | 5/0 | Slightly less |
| 3 | 145/90 | 110/70 | 35/20 | 155/100 | 135/100 | 20/0 | Slightly less |
| 4 | 145/90 | 125/80 | 20/10 | 155/100 | 140/100 | 15/0 | Slightly less |
| 5 | 125/80 | 105/70 | 20/10 | 135/90 | 135/90 | 0/0 | Less |
| 6 | 135/80 | 105/65 | 30/15 | 150/100 | 130/90 | 20/10 | Slightly less |
| 7 | 140/70 | 95/55 | 45/15 | 160/90 | 190/70 | 20/20 | Slightly less |
| 8 | 150/90 | 105/75 | 45/15 | 155/100 | 125/95 | 30/5 | Slightly less |
| 9 | 135/70 | 100/55 | 35/15 | 145/80 | 115/70 | 30/10 | Slightly less |
| 10 | 150/90 | 75/50 | 75/40 | 155/100 | 110/80 | 45/30 | Less |
| 11 | 110/75 | 110/75 | 0/0 | 150/90 | 150/90 | 0/0 | Same |

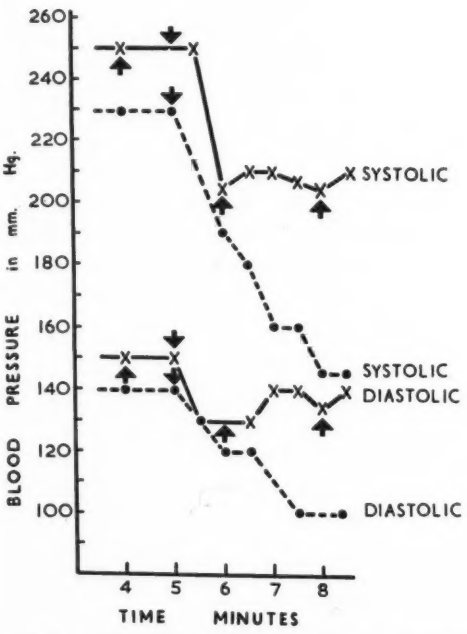


FIG. 3. The effect of experimental elevation of the blood pressure by a humoral agent upon the fall of blood pressure from the subsequent administration of hexamethonium. Blood pressure falls (horizontal posture) in a hypertensive patient following a large intravenous injection of hexamethonium ↓. ●------● under control conditions. ×——× during blood pressure elevation induced by injections at 2-minute intervals of ↑ angiotonin. The upper two curves are systolic and the lower two diastolic pressures.

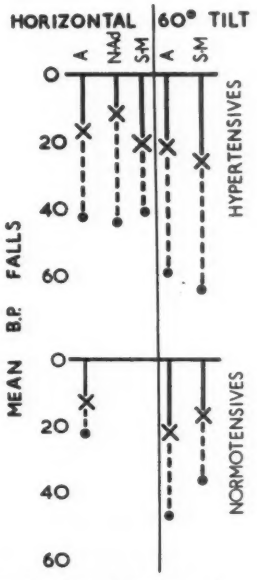


FIG. 4. The lengths of the lines down to the dots represent the falls of blood pressure from large intravenous doses of hexamethonium. The lengths of the lines down to the crosses represent the smaller falls of blood pressure from the same doses of hexamethonium when the blood pressure has been first raised to a higher level by intravenous injection of a pressor agent. Each line represents the mean of 10 to 12 experiments. The results obtained with angiotonin are marked "A", with noradrenaline "N-Ad", with s-methyl *iso*-thiourea "SM". "Horizontal" and "60 degree tilt" refer to the positions of the patients during the investigation. Results on hypertensives and normotensives are set out separately.

and the mean residual diastolic blood pressure was 67 mm. Hg (S. D. ± 11).

(c) *Modification of the Depressor Effect of Hexamethonium by Pressor Substances in Hypertensive and Normotensive Subjects*

In 60 patients the effects of hexamethonium under resting conditions were compared with the effects of the drug after the blood pressure had first been raised by the continued administration of angiotonin, s-methyl *iso*-thiourea or noradrenaline. The pressor substance was given first and the administration continued until a steady blood pressure had been obtained. The blood pressure was usually about 20 mm. Hg higher than the resting level. The effective dose of hexamethonium was then given. In all the tests the fall of blood pressure was much smaller after the administration of a pressor agent than under resting conditions. Similar results were obtained both with the patients recumbent and on a tilting table at 60 degrees with the legs down, although the falls of blood pressure were usually still greater in the tilted position than with the subject recumbent.

It is clear from our observations that, although the initial level of the blood pressure had been raised by the pressor agent, the falls of blood pressure produced by hexamethonium were then smaller than under resting conditions. Detailed results of some of the individual experiments are shown in tables 1 to 5 and typical falls of blood pressure are shown in figures 3 and 4.

## Discussion

Our results have confirmed the work of others, that the falls of blood pressure after ganglionic blockade are usually much greater in hypertensive subjects than in those with normal blood pressures. It is of interest that patients with hypertension due to renal disease and to postpregnancy toxemia often have falls of blood pressure as large as those in subjects with essential hypertension. Indeed, there does not seem to be any correlation between the clinical manifestations of the hypertension and the response to ganglionic blockade. In particular, the fundal changes do not offer a guide as to the likelihood of greater or smaller blood pressure falls with hexamethonium.

We shall point out later that there appears to be some doubt about the mechanism of action of hexamethonium, and in particular about its action on the cardiac output. It is evident, however, that hexamethonium acts by the removal of a neurogenically maintained fraction of the blood pressure and from our results it is evident that the neurogenically maintained fraction is greater in the average patient with hypertension than it is in health.

It has been shown that when in hypertension or health, a humoral vasoconstrictor, such as angiotonin, is administered, the subsequent administration of a ganglion blocking agent induces much smaller blood pressure falls. It seems likely that the reaction of the blood pressure control mechanisms to the administration of a pressor agent is to decrease the neurogenic component. Under such circumstances, when there is less of the neurogenic component to be removed, it is found, as might reasonably be expected, that smaller blood pressure falls follow ganglionic blockade.

There has never been any real doubt that the homeostatic mechanisms continue to operate in patients with hypertension. The present study has indicated that there is a reciprocal relationship between the neurogenic and nonneurogenic components in maintaining a raised blood pressure level. It seems that the neurogenic component fluctuates with changing circumstances so that nonneurogenic changes in the level of the blood pressure are to some extent buffered by the neurogenic changes. Thus, without very much change in the level of the blood pressure, there may be considerable fluctuation in the proportion of the neurogenic and nonneurogenic components. For example, after ganglionic blockade, when there is no compensatory adjustment by neurogenic means, the assumption of the erect posture leads to an important decrease in the level of the blood pressure measured in the arm. It seems that normally as the effect of the nonneurogenic component decreases with assumption of the erect posture, the effect of the neurogenic component increases, so that normally there is little change in blood pressure

with change of posture. There is, however, a considerable change of proportion in the effects of the neurogenic and nonneurogenic components with change of posture. It is clear that in the vertical posture, not only does the effect attributable to the neurogenic fraction increase, but the effect of the nonneurogenic fraction decreases. Because of this, both in normotensives and in hypertensives, hexamethonium causes greater falls of blood pressure in the erect posture for more neurogenic impulses are concerned in the maintenance of the blood pressure level in this posture.

Our findings are inconsistent with the view so commonly expressed that stimuli applied when the blood pressure is high are likely to induce changes which are larger because they are in proportion to the degree of blood pressure elevation. On the contrary, we find that in one and the same patient, the blood pressure fall from hexamethonium is decreased if the blood pressure is first raised by a pressor agent. In other words, the constriction of the blood vessels by a humoral agent reduces and does not exaggerate the neurogenic vasoconstriction. It seems from our observations, therefore, that falls of blood pressure occurring with hexamethonium are not exaggerated by the fact that the starting level of the blood pressure is high, so that the observed increase in the blood pressure fall in hypertensives may be taken to indicate an increase in the neurogenic component, and the observed increase in the level after ganglionic blockade may be taken to indicate an increase in the nonneurogenic component.

It might be argued that the acute administration of angiotonin or other pressor substances leads to a different response than that which would occur with the continued presence of these agents. Our observations on the depressor action of hexamethonium, however, also lead us to the conclusion that the nonneurogenic and neurogenic components vary in a reciprocal manner; for although there is a correlation between the height of the blood pressure and the response to hexamethonium, we have also found that a high residual blood pressure tends to be associated with a smaller neurogenic component, both in hypertension and in health. Thus, both in our acute experiments with pressor substances and in chronic hypertension the elevation of the blood pressure by nonneurogenic means seems to lead to a decrease, rather than an increase, in the neurogenic fraction.

The further interpretation of our results is made difficult by the fact that the mechanism of the blood pressure fall resulting from ganglionic blockade with hexamethonium is in dispute. Some workers maintain that it is due almost entirely to a reduction in the peripheral resistance with little change in the cardiac output.[5, 7, 9] Others have found, however, that the cardiac output often falls.[8, 10, 13] It is generally conceded that if the cardiac output falls it does so as a result of peripheral vasodilatation leading to pooling of blood in the extremities. If the fall in cardiac output is assumed to be the cause of the blood pressure fall after ganglionic blockade it would be to be expected that the blood pressure fall would be proportional to the initial level of the blood pressure, for by Poiseuille's law a reduction in the cardiac output would ordinarily lead to a larger fall in blood pressure if the peripheral resistance were high than if it were low. It would be expected, therefore, that a fall in cardiac output would lead to a larger fall of blood pressure in the hypertensive subject whether the arteriolar constriction was primarily neurogenic or primarily humoral. In our experiments, however, an increase in the amount of circulating pressor substance led to a reduction of the depressor action of hexamethonium. If indeed the action of hexamethonium is to reduce the cardiac output, then we have to explain why this action is antagonized by the humoral pressor substances which we have used. The best explanation would seem to be that an important part of the action of the humoral pressor substances used is exerted on the vessels whose dilatation leads to a fall in cardiac output. Thus, it might be that an important part of the action of angiotonin or similar substances is exerted on the veins, so that to a great extent neurogenic venous tone can be replaced by humoral venous tone. If this is so the presence of humoral pressor substances might prevent or reduce the amount of

venous pooling which usually follows ganglionic blockade. Such a conclusion might account for the observations of Freis and coworkers[8] that in some patients with malignant hypertension or hypertensive heart failure, hexamethonium causes no fall in cardiac output; whereas in subjects with essential hypertension the cardiac output falls. In any case, whether these pressor substances act on arteries or veins or both, their effects are to antagonize the effects of ganglionic blockade and to diminish the neurogenically maintained fraction of the blood pressure.

Our experiments are consistent with the already strong evidence that in established hypertension the vasomotor centres continue to regulate blood pressure levels both in an upward and in a downward direction. Our experiments with angiotonin and hexamethonium suggest that the effects of pressor stimuli are still opposed by homeostatic decreases of sympathetic tone and factors tending to reduce the blood pressure, such as the erect posture, or falls of cardiac output, are countered by increases of sympathetic tone. It may be worth considering the possibility, admittedly speculative, that rises of blood pressure imposed by a variety of primary causes, some perhaps physiological, and others pathological, lead in the course of time to a displacement of the centre's activity so that, while continuing to regulate, it does so mainly in a higher range. Some explanation is needed for the fact that in almost all kinds of continued hypertension the vasomotor centre remains active and opposes both pressor and depressor stimuli. Evidence for the view that this change in the level of response of the vasomotor centre may have resulted from long exposure to the effects of raised blood pressure is the fact that this change in the vasomotor centre appears to occur in all forms of hypertension, even of the most varied aetiology. Without an explanation of this sort it is difficult to explain such changes occurring in nephritis, pregnancy toxemia, essential hypertension, pyelonephritis, and other less common causes of high blood pressure in man.

If the evidence for increased vascular reactivity in hypertension cited by Doyle and Black[14] be confirmed, it becomes evident that both normal and pathological vasopressor influences will have a greater effect upon the blood pressure in hypertension than in health and will demand correspondingly greater attempts at homeostasis. The vasomotor centres have functions concerned with postural adjustments and distribution of blood which demand bidirectional adjustments. Unless an alteration in the homeostatic level of the blood pressure control centres occurred it seems likely that an increase in vascular reactivity would imply that only unidirectional (downward) control could be exercised.

## Summary

1. Blood pressure falls in the horizontal posture were induced by large intravenous doses of hexamethonium.

2. In normotensives as well as hypertensives the blood pressure falls are greater when the initial blood pressure level is high than when it is low. The blood pressure falls are much greater in hypertensive than in normotensive subjects.

3. In normotensives and hypertensives it is found that those patients with high floor (residual) blood pressures (after the hexamethonium) have smaller blood pressure falls than patients with low floor blood pressures.

4. In normotensives and in hypertensives elevation of the blood pressure by the administration of angiotonin, noradrenaline or s-methyl *iso*-thiourea leads to a decrease in the extent of the blood pressure fall which may be obtained by the intravenous administration of hexamethonium.

5. The above evidence makes it unlikely that the enhanced response to hexamethonium observed in most of our hypertensive patients could be merely the result of an increase in the blood pressure brought about by circulating pressor agents. The results, while in no way excluding the participation of humoral factors, are more consistent with the hypothesis that, in most hypertensives, the blood pressure elevation is predominantly the result either of an increase in the nervous stimulation of blood vessels or in an increase in the reactivity of blood vessels to nervous stimulation.

6. It is pointed out that in health and in hypertension an alteration in the neurogenically maintained fraction of the blood pressure is the principal means by which blood pressure levels are regulated.

7. The prompt response of the homeostatic mechanisms to assumption of the erect posture consists of an increase in the neurogenically maintained fraction of the blood pressure, to compensate for the gravitational decrease in the effect (at arm level) of the nonneurogenically maintained fraction. Likewise, in normotension and hypertension the response of the homeostatic mechanism to the horizontal posture or to the administration of a pressor drug consists in a compensatory decrease of the neurogenically maintained fraction of the blood pressure.

8. The smaller blood pressure fall from hexamethonium when the subject is in the horizontal posture and the decrease in the extent of the fall when the hexamethonium is given after administration of a pressor substance are both explained in terms of decrease in the amount of neurogenically maintained vascular tone which is available to be removed when the hexamethonium is administered.

9. It is not settled to what extent decrease in neurogenic vascular tone (by hexamethonium) affects the peripheral resistance by its action on arterioles, or the cardiac output by its action on veins and capillaries.

10. It seems likely that continued exposure to blood pressure elevation from a variety of primary causes may lead to upward displacement of the activity of the vasomotor centre, so that while continuing to regulate it does so mainly in a higher range.


### Summario in Interlingua

Le magnitude del reduction del pression sanguinee, le qual se manifesta in positura horizontal post le administration intravenose de hexamethonium, monstra que un importante parte del elevation del pression sanguinee in patientes con hypertension essential es mantenite neurogenicamente. Quando le pression sanguinee es initialmente altiate per angiotonina o altere agentes pressorial, le subsequente responsa a hexamethonium es grandemente reducite. Simile responsas es observate in individuos normo- e hypertensive. Isto es causate per le reduction del centros regulatori que compensa le effecto del agente pressorial per reducer le componente neurogenic. Le resultante reduction del neurogenicamente mantenite fraction del pression sanguinee reduce le responsa a hexamethonium. Nos avantia le hypothese que in le curso del tempore un prolongate exposition a stimulos pressorial induce le centros vasomotor a exercer lor function regulatori a un nivello superior al nivello normal.



### Acknowledgment

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# Studies in Intravascular Coagulation

## IV. The Effect of Heparin and Dicumarol on Serum-Induced Venous Thrombosis

*By* Stanford Wessler, M.D. and Leslie E. Morris, M.D.

With the Technical Assistance of Carol Ho and Joan Moran

A method has been previously described whereby the infusion of canine serum and serum fractions rich in convertin, but essentially devoid of thromboplastin, prothrombin, ac-globulin and thrombin, initiates venous thrombosis in dogs at sites of partial or complete venous stasis far removed from the site of infusion. It has been suggested that the pathogenesis of venous thrombosis in various clinical states may be referable to local stasis combined with a transient increase in circulating convertin activity. The present study demonstrates that heparin is superior to dicumarol in inhibiting the evolution of such serum-induced intravascular thrombi in dogs.

In a previous study the infusion of heterologous, canine serum or serum fractions rich in convertin (SPCA) was shown to initiate venous thrombosis in dogs at sites of partial or complete stasis far removed from the site of infusion.[1] It was suggested, as a working hypothesis, that the pathogenesis of venous thrombosis in various clinical states might be referable to local venous stasis combined with a transient increase in circulating convertin activity.[1]

To gain further insight into the clot promoting effect of serum and the efficacy of anticoagulant drugs, the role of Dicumarol and heparin in blocking the evolution of serum-induced venous thrombosis was studied in dogs.

### Methods and Material

Intravascular thrombosis can be routinely induced in untreated animals by a technic previously described.[1] Briefly, in dogs under sodium pentobarbital anesthesia, a segment of jugular vein 3 to 6 cm. in length was freed from its surrounding structures and its tributaries ligated. Thirty cc. of a barium sulphate eluate of serum* rich in convertin but essentially devoid of thromboplastin, prothrombin and thrombin was then infused into a distant antecubital vein. One minute later, after the infused serum eluate had been dispersed throughout the circulation, the previously freed jugular segment was gently isolated with 27 mm. seraffine clamps. A large red clot was routinely formed in the isolated vein segment within 60 seconds after clamping. Similar clots were readily induced with 90 cc. of canine serum but not with canine plasma.

Convertin is one of the factors necessary for normal coagulation in man, and is found in appreciable amounts in serum stored for 24 hours at 4 C. Current knowledge does not permit definition of SPCA as one or more distinct substances. For the present, it can be described as an entity which, though distinct from ac-globulin, is also essential for the physiologic conversion of prothrombin.[2, 3] A precursor of convertin, proconvertin (pro-SPCA), is present in plasma. During coagulation proconvertin is converted to convertin. The in vitro tests used in this study, however, do not distinguish between the inactive and active forms but measure the total amount of convertin complex present in a given sample.[4] The failure of plasma to induce clotting in the isolated venous segment sug-

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* This fraction was obtained by adding barium sulphate to serum, shaking the mixture, decanting the supernatant liquid, washing the barium sulphate with acetate buffer, eluting the convertin SPCA with sodium citrate and dialyzing this eluate against tap water.[1]

TABLE 1.—*Overall Prothrombic Activity, Convertin (SPCA) and Prothrombin Concentrations in Thirteen Dogs 72 to 96 hours after receiving 3.6 to 4.5 mg. Dicumarol per Kg*

| Dog # | Overall one-stage prothrombic activity[5] (% of Normal) | Convertin[4] (% of Control) | Two-stage prothrombin concentration[6] (% of Control) | One-stage prothrombin concentration[7] (% of Control) | Clot in Vein |
|---|---|---|---|---|---|
| 1 | <1% | <1% | 14% | 34% | 0 |
| 2 | <1% | <1% | 13% | 44% | 0 |
| 3 | <1% | 0% | 10% | 21% | 0 |
| 4 | <1% | 0% | 12% | 27% | 0 |
| 5 | <1% | <1% | 2% | 11% | 0 |
| 6 | <1% | <1% | 4% | 11.5% | 0 |
| 7 | <1% | <1% | 4% | 9% | 0 |
| 8 | <1% | <1% | 3% | 13% | 0 |
| 9 | <1% | <1% | 3% | 10% | 0 |
| 10 | <1% | <1% | 3% | 6% | + |
| 11 | <1% | <1% | 6% | 10% | 0 |
| 12 | <1% | <1% | 4% | 11% | 0 |
| 13 | <1% | <1% | 8% | 15% | 0 |

Serum-induced thrombosis occurred in all but one dog; in this animal the coagulation defect was so severe that the clotting time had been tripled.

gests, however, that the effects observed are not attributable to proconvertin but rather to its activated form, convertin.

In the experiments to be described, established methods were used to determine the overall one-stage plasma prothrombic activity,[5] prothrombin,[6, 7] ac-globulin,[8] convertin[4] concentrations and clotting times.[9]

## DATA

Dicumarol was administered to 13 dogs in a single oral dose ranging from 3.6 to 4.5 mg. per Kg. Following reduction of the overall one stage prothrombic and convertin activities to 1 per cent or less of the control values (table 1), 30 cc. of the serum eluate was injected through an antecubital vein, and a previously-freed jugular vein segment then isolated in the usual manner.* Despite the profound, induced clotting deficit and hemorrhagic diathesis before and during surgery, thrombus formation, indistinguishable from that found in untreated animals, was observed in all but one dog; in this animal the coagulation defect was so severe that the clotting time had been

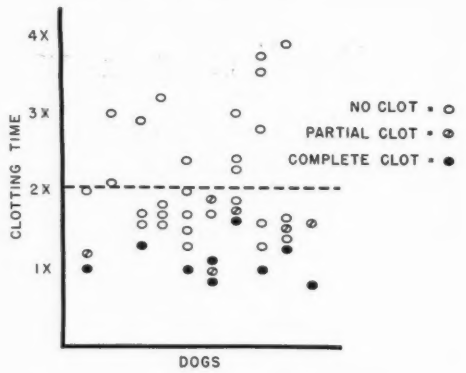


FIG. 1. Relation of clotting time to development of serum-induced thrombosis in dogs receiving heparin. Each vertical column refers to determinations in a single animal. So long as the clotting time exceeded twice the control value, intravascular clotting did not occur. Even below this level some interference with thrombus formation could still be demonstrated.

trebled. In these dogs, toxic from Dicumarol, the ac-globulin concentration was normal, and appreciable amounts of plasma prothrombin were present. Thus the marked reduction in the one-stage activity reflected primarily the absence from the circulation of the convertin complex.

The effect of heparin was similarly studied in 10 dogs. After control clotting times were obtained, the animals were given 0.23 mg. of heparin per Kg. intravenously. At varying intervals after the injection, 30 cc. of the serum eluate was injected through an antecubital vein, and a previously freed vein segment was then isolated in the standard manner. At the moment of each vein isolation, the clotting time was determined. Thirty cc. aliquots of the serum eluate were injected at 15 to 30 minute intervals,* followed in each instance by the isolation of a previously freed vein segment until a clot was obtained. As indicated in figure 1, so long as the clotting time of the animals exceeded twice the control value, the serum eluate never induced intravascular clotting. Even below this level some interference with thrombus formation could still be

* All experiments were performed 72 or 96 hours after the ingestion of Dicumarol.

* Ten minutes after the infusion of the serum eluate its clot promoting activity is dissipated.[10]

demonstrated in some animals by the finding of only small, fragmented clots. Compared with the extensive operative bleeding in the dogs receiving Dicumarol, the relative lack of hemorrhage during surgery in the animals receiving heparin was noteworthy.

## Discussion

When 30 cc. of a serum eluate rich in convertin is infused into an antecubital vein of a normal anesthetized dog, no detectable increase in the convertin content of jugular vein plasma or serum can be demonstrated during or following the infusion. The failure to detect a rise in the convertin activity of jugular vein plasma or serum may be explained by the large dilution of the infused material in its passage through the circulation from the antecubital to the jugular vein. In any event, an amount of convertin, not measurable by present technics and infused into animals themselves essentially devoid of convertin, induces extensive intravascular coagulation. On the other hand, the infusion of the same amount of convertin in animals with a normal level of convertin, in which heparin administration has only doubled the clotting time, does not induce clotting.

There is additional experimental evidence to support the view that heparin has greater anticoagulant properties than does Dicumarol. In contrast to the efficacy of heparin, we have demonstrated that severe Dicumarol-induced hypoprothrombinemia and convertin deficiency does not retard spontaneous fibrin deposition in an isolated segment of vein,[11] and does not effectively block clot production by trypsin,[12] thrombin[10] or thromboplastin.[10] We believe the significance of this cumulative experience lies in the observation that substances such as Dicumarol, which depress that part of the coagulation sequence concerned with prothrombin conversion may not provide as optimal an anticoagulant effect as heparin-like compounds which block fibrin deposition through other mechanisms.[13-16] These studies also suggest that heparin may have, in addition to its other properties, a specific anticonvertin effect.

It is not unlikely that the pathogenesis of intravascular thrombosis may be different in different clinical states. It has been suggested that convertin may play a key role in thromboembolism.[17, 18] Several investigators have in fact demonstrated a temporary rise in the convertin complex of human pregnant and postpartum plasma.[19-22] In an earlier report from this laboratory,[1] direct experimental evidence showed that serum fractions rich in convertin may, in dogs, initiate venous thrombosis at sites of partial or complete stasis. The experiments described herein indicate that if convertin is a responsible initiating agent in vascular thrombosis in man, heparin, in contrast to Dicumarol, may provide more effective protection against the induction or propagation of such clots.

## Summary

Convertin (SPCA) may play a key role in initiating venous thrombosis in some clinical states. In dogs, heparin is superior to Dicumarol in blocking the evolution of intravascular thrombi induced by canine serum fractions rich in convertin.

## Summario in Interlingua

Convertina (accelerator del conversion de prothrombina seral) ha possibilemente un function decisive in le initiation de thrombosis venose in certe statos clinic. In canes, heparina es superior a Dicumarol como agente blocator del evolution de thrombos intravascular inducite per fractiones de serum canin ric in convertina.

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# Changes in Cardiac Output with Age

*By* MARTIN BRANDFONBRENER, M.D., MILTON LANDOWNE, M.D. AND NATHAN W. SHOCK, PH.D.

In the first of two papers, the details and results of a systematic, carefully standardized application of dye dilution technic to the measurement of cardiac output are reported. A substantially reduced output was a consistent finding in older subjects. Factors responsible for this are analyzed in this article, and further interpretations are made in the succeeding article. One result of the analysis of time-concentration curves of dye provides an interesting relationship to clinical estimates of circulation time.

INVESTIGATIONS of cardiac output in older, but presumably "normal," adults were made by Starr and his coworkers,[1] by Lewis[2] and by Apéria[3] 16 to 20 years ago, using the indirect gas methods then available. Although the insensitivity of these methods could mask a sizeable change, Starr and his associates noted that in the "period before 20 years the average cardiac index is higher than at any time later, after 50 it slowly declines. The number of cases was too small to demonstrate the significance of the difference." Their series included only nine cases over 50 years of age; the oldest was 76. Lewis, in a systematic agewise study, found a small decrease in cardiac index in 100 male subjects between 40 and 89 years of age. He considered that the observed changes represented neither statistically nor physiologically a significant decline and that they were predominantly the result of a decrease in oxygen consumption. A decrease of about the same order may be calculated from the data reported by Apéria,[3] utilizing the acetylene technic of Grollman. These indirect Fick gas methods are now recognized as yielding values which are approximately 25 per cent too low, but even allowing for this, a sizeable decrease in cardiac output cannot be said to have been demonstrated by these studies, despite a consistent suggestion in this direction.

Age comparisons, using the Fick principle with right heart catheterization, were sought in the studies of Stead and his colleagues,[4] Cournand and his co-workers[5] and Nickerson and associates.[6] In the series of Stead and associates,[4] the oldest subject was 39 years. Cournand and co-workers[5] included 17 normal male subjects, the oldest of whom was 58 years. Among these there was a definite decrease in cardiac output with age. Nickerson and associates[6] studied seven patients over 50 years old, the oldest being 57, but found no significant age change. Other studies, where cardiac catheterization was used, do not contain the number or range of subjects to provide agewise data.

In a recent report, Smith and colleagues,[7] using an indicator dilution technic, obtained a mean cardiac index of 2.67 in 10 subjects age 62 to 77 years, average 71 years. They considered this to be an unexpectedly low value in comparison to a mean of 3.5 liters per minute for 10 subjects 22 to 55, average 52 years of age.

Many attempts to estimate cardiac output have been made by approximation formulas or by empiric constructions based on blood pressure, pulse[8, 9] or ballistocardiographic records.[10, 11] These methods do not measure cardiac output, nor do they provide reliable estimates for the individual. With the availability of an indicator dilution method for the determination of cardiac output, we set about to investigate this problem.

## METHODS

*Subjects.* Determinations of cardiac output by an indicator dilution method were made in 67 males between the ages of 19 and 86 years of age, (average age 52.5 years). According to clinical criteria these subjects were free of suspected relevant disease and they form the basis for an analysis of agewise change. Satisfactory duplicate determinations of

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cardiac output were performed in 53 of these subjects. Seven additional subjects who were not considered "normal" were added to provide a series of 60 subjects on whom reproducibility of the procedure was tested. These seven are not included in the agewise analysis. All patients were chosen from the wards of the Baltimore City Hospitals, after having been in the hospital and afebrile for at least five days prior to the test procedure. They were ambulatory and none had had any surgical procedure within five days prior to the test. Some were convalescing from respiratory infections or awaiting discharge after convalescing from orthopedic conditions. Many had recovered from acute illnesses months or years ago and were living in the Infirmary division of the Baltimore City Hospitals. All subjects were interviewed by one of the investigators (M. B.). None presented histories compatible with cardiovascular disease or had symptoms clearly referable to the cardiovascular system such as angina, orthopnea, exertional dyspnea, palpitations, persistent or evident ankle edema. None had ever taken any cardiotonic drugs. On physical examination, subjects showing evidence of valvular disease or aortitis, cardiac enlargement, significant arrhythmia, congestive failure, hypertensive disease or a casual brachial blood pressure exceeding 175 systolic or 90 mm. Hg diastolic were excluded; diabetic, hyperthyroid, anemic or immobile patients were also excluded. For this purpose anemia was judged by an arterial hematocrit below 33 per cent (with one exception, a subject 80 years of age whose hematocrit was 28 per cent*).

Venous pressure measured in an antecubital vein, using a 15 gage needle, was less than 12 cm. above the level of the atrium in all cases. Decholin circulation time was performed in all subjects and an ether circulation time was performed in approximately half of the subjects. Subjects with decholin circulation times as high as 30 seconds were not eliminated on this basis alone. All subjects in this series had recent electrocardiograms which were within normal limits as judged by the criteria of Burch and Winsor[13]. A teleoroentgenogram of the chest was obtained on each subject, and cases showing any pulmonary or mediastinal lesions suspected of being acute or extensive were excluded. The long and broad diameters of the cardiac silhouette were measured and no subject was included in the series, if the product of these measurements exceeded by 15 per cent the value predicted on the basis of the individual's height and weight.[14]

* Brannon and associates[12] have shown that the cardiac output does not change unless the hemoglobin falls to a level of about 7 Gm. The included 80 year old subject whose hematocrit was 0.28 had a cardiac output which was not significantly different from the mean for his age group.

*Procedure.* The patients were in the basal state preceeding the test. After novocaine infiltration, a 15 cm. long polyethylene catheter was placed in a right antecubital vein and a thin wall 18 gage needle was placed in the left brachial artery. Cardiac rate and intra-arterial pressure were recorded before each determination of cardiac output. Approximately 5 mg. of Evans blue dye was delivered into the circulation through the catheter from a calibrated syringe, and blood was sampled from the brachial artery by a collection device similar to that described by Newman and co-workers.[15] In most subjects a second determination was made 10 minutes after the completion of the first.

The optical density of the dyed serum was read promptly in microcells on a Beckman Model DU spectrophotometer at 620 mμ. The characteristics of the dye curves were read from concentration-time plots made on semilogarithmic paper. Determinations were also excluded from this series if the subject obviously was not basal, for example, if he coughed, moved about, or complained during the procedure.

### *Calculations*

We have attempted to use terms and symbols consistent with the recent literature.[16, 17] The data and derived values in the tables are based upon an average of one to three separately determined values for each item.

$$\textit{Cardiac Output } (C.O. = \frac{60\ q}{A} \textit{ liters per minute})$$

where $q$ is the quantity of indicator dye injected in milligrams and $A$ is the area under the time concentration curve in the absence of recirculation in milligrams per second per liter, derived by extrapolation and calculated by summation.[18] Curves where extrapolation was uncertain, such as those with less than four points on the section of decreasing concentration prior to recirculation, were eliminated.

*Heart Rate* in beats per minute was measured as the reciprocal of the average cycle length of 10 consecutive brachial arterial pressure pulses recorded just before each determination of cardiac output.

*Dye appearance time* (*A.T.*) is the time in seconds between the beginning of injection and the time ($t_a$) at which a detectable *increase in dye* concentration (0.1 mg. per liter) occurred in a sampling tube. *Dye passage time* (*P.T.*) is the time in seconds between $t_a$ and the time ($t_d$) at which estimated relative dye concentration had declined to 0.1 mg. per liter eliminating the estimated effect of recirculation. *Mean time of a lag exponential* $\left[(T_{1e}) = A.T. + \frac{1}{K}\right]$ where *A.T.* is the appearance time and $\frac{1}{K}$ is the reciprocal slope of the extra-

polated log concentration-time curve in seconds. *True mean transit time* ($T$) in seconds is obtained by summing the products of each blood sample concentration and its time and then dividing by the summed concentrations under the curve, i.e. the expression which closely approximates the

$$\bar{T} = \frac{\sum_{t_a}^{t_d} tc\Delta t}{\sum_{t_a}^{t_d} c\Delta t}$$

theoretic formula.[16]

*Central Volume* ($V$) was calculated as the product of cardiac output ($C.O.$) and mean time ($\bar{T}$).

The statistical analysis and symbols used generally follow standard procedure.[19] The statistics of simple linear regressions have been used as a convenient means of displaying results. To develop consistent expressions for some interrelated items, we have obtained linear regressions of logarithmic values. There is, however, no implication that either a linear or exponential relationship exists, in any or all measures, and our probability estimates are not substantially altered by either type of fit.

The predicted value at 50 years of age ($\hat{Y}_{50}$) has been selected in preference to the mean value ($\bar{Y}$), as a basis of representation for comparison of items showing age trends: $\hat{Y}_{50} = Y - b\Delta a$, or $\hat{Y}_{50} = \bar{Y}e^{-b\Delta a}$, where $\Delta a$ equals mean age minus 50 years and $b$ is the coefficient of regression. From the linear expression, the average rate of change may be conveniently expressed as per cent of the 50 year value; $\left(\frac{100\ b}{\hat{Y}_{50}}\right)$ and the predicted value ($\hat{Y}$) at any age: $\hat{Y} = \hat{Y}_{50} + b\Delta a$, where $a$ equals age minus 50 years. From the exponential expression, $100 \times$ *the regression coefficient* ($b$) represents the average per cent change per year, and the predicted value $(\hat{Y}) = \hat{Y}_{50}\ e^{ba}$. An estimate of the error of a single determination was calculated as $\sqrt{\frac{\Sigma(Y_1 - Y_2)^2}{2N}}$ from duplicate determinations made on the same subject.

## Results

In the 60 subjects for whom there were successful duplicate determinations, the estimated error of a single observation was 345 ml. per minute or 6.4 per cent, the difference between these two determinations in the same individual without regard to sign averaged 400 ml. per minute, or 7.9 per cent of the mean of the pair.*

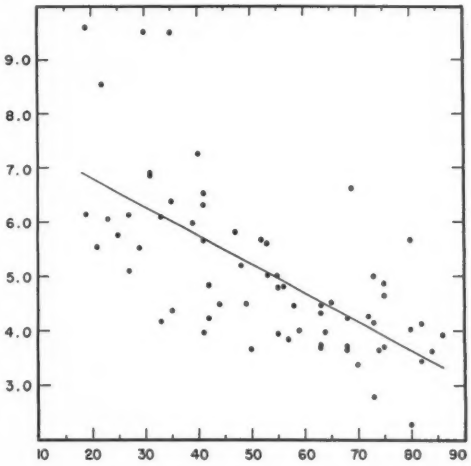


FIG. 1. The relation between cardiac output and age in 67 'basal' males without circulatory disorder. Each point represents the average of two measurements in 49 subjects, of three measurements in four subjects, and a single measurement in 14 subjects. The line indicates the simple linear regression for the data in all figures. Figs. 1, 2, 3 and 5, are plotted on comparable ordinate scales by making the ratio of scale unit to mean value similar in these figures.

It is of interest that the absolute deviation between determinations varied directly with the magnitude of the cardiac output ($r = 0.40$) while the per cent difference was more constant.

Although the mean value of the first determination exceeded that of the second by 136 ml. per minute ($\sigma_d = 501$)†, this difference was not statistically significant. The first value exceeded the second in 34 cases but was less in 26 cases. There was also no evidence of an age trend in the difference.

*Cardiac Output* (C.O.)—The basal cardiac output for all subjects averaged 5.08 liters per

* In initial studies on the validation of the dye technic in our laboratory, Dr. Harold Silver performed a preliminary series of replicate determinations upon 16 patients, using essentially the same technic except for a manually operated collection rack instead of the rotating disc. The average difference between pairs was also 400 ml. or 7.4 per cent of the mean of the pairs, and all values in this group except two agreed within 19 per cent. The estimated error of a single determination was 437 ml. per minute or 7.4 per cent. Smith and associates[7] included a study of reproducibility in a recent report. Thirty-one of 34 pairs repeated within 40 minutes agreed within 15 per cent. Duplicate determinations were also reported by Cugell[20] in four patients.

† $\sigma_d$ = standard deviation of the distribution.

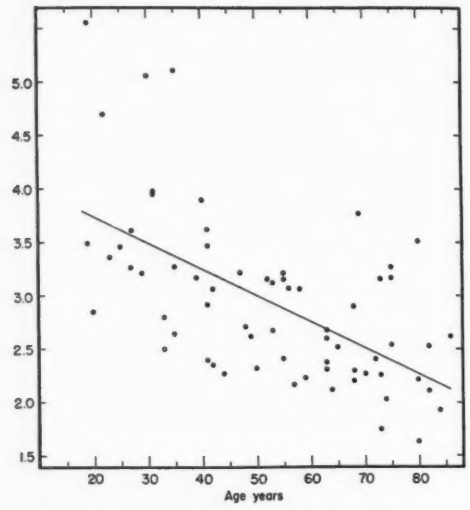


FIG. 2. Cardiac index versus age. Legend as in figure 1.

minute ($\sigma_d$ = 1.51). Table 1 lists salient data for the decade means* with their standard deviation of the means. Figure 1 shows a scatter plot of the individual means. A decline in cardiac output is evident after the third decade. The coefficient of correlation of log C.O. with age for all data was highly significant ($r$ = −0.69) and the regression of cardiac output on age averaged 1.0 per cent per year. While the per cent standard deviation of the distribution† was 31.4, the per cent standard deviation about regression§ was substantially less, 21.8.

The *cardiac index* for all subjects (table 1) averaged 2.94 liters per minute per square meter of body surface area, ($\sigma_d$ = 0.78). Figure 2 shows a scatter plot, and table 1 shows the mean index by decades to decrease with age in a manner similar to the fall in cardiac output. The age regression averaged 0.79 per cent per year.

Table 1 shows a small agewise decrease in the decade means of calculated *surface area* of this group of subjects. The decrease is small but is statistically significant with a regression of −0.22 per cent per year. The total variation of surface area in the material was small with a standard deviation of ±.17 M.², but nevertheless cardiac output showed a correlation of 0.43 with surface area, indicating that this method can differentiate the large from the small individual.

The average *stroke volume* (table 1) was 74.2 ml. per beat, ($\sigma_d$ = 18.9). With two exceptions, the means of stroke volumes for each decade tend to diminish progressively. The overall correlation of age and stroke volume was high with an average decrease of 0.70 per cent of the beat output per year. The correlation of age and stroke volume was less striking than was the correlation of age and cardiac output, due to an agewise decrease in heart rate in these subjects. Thus the age decline in cardiac output per minute is in part attributable to an observed reduction in body size (surface area) and in part to a reduction in heart rate. When the *stroke index* (stroke volume per unit of surface area) was computed, the mean value was 43. ml. per beat per square meter ($\sigma_d$ = 9.5) and the residual diminution with age is still highly significant at 0.49 per cent per year. A scatter plot is shown in figure 3. The foregoing, and other significant correlations and statistical analyses are summarized in table 2.

The interrelationships of cardiac output and age in our series may also be expressed as if the factors contributed by surface area and heart rate were removed, by the coefficient of partial correlation for cardiac output and age which was −0.50.

Although less conventional, it is at least equally applicable, and even more convenient, to express this data on the basis of body weight instead of surface area. The coefficient of variability is not lessened, nor is the simple correlation coefficient with age improved and the coefficient of partial correlation is −.54.

*Estimates of circulation velocity and central volume.* The appearance time (A.T.) of dye in the limb opposite to the injection site may be considered as an objective test of "circulation time". This averaged 14.1 seconds, ($\sigma_d$ = 2.6).

* At the request of the editor, the individual data have been omitted from table 1. These data will be furnished by the authors on request as long as copies are available. They have also been deposited with the Photoduplication Service, Library of Congress, Washington 25, D. C. as Document No. 4675.

† 100 (antilog $\sigma_{d\log c.c.}$ − 1.0).

§ 100 [antilog $\sigma_{d\log c.c.}$ $(\sqrt{1.0 - r^2})$ − 1.0]

TABLE 1.—*Summary of Results by Decades*

| | Age | $n$ | Surface, Area, M.² | Heart Rate/min. | Cardiac Output, Liters/min. | | | Cardiac Index, L./min/ M.² | Stroke Volume, ml./beat | Stroke Index, ml./beat/ M.² | Appearance Time, seconds | Mean Transit Time, seconds | Passage Time, seconds |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | I | II | Aver. | | | | | | |
| Mn. | 23.6 | 9 | 1.75 | 76.9 | 6.65 | 6.04 | 6.49 | 3.72 | 85.6 | 48.9 | 12.0 | 19.0 | 26.1 |
| $\sigma_{Mn.}$ | | | .04 | 4.6 | | | .51 | .28 | 6.1 | 3.1 | .7 | 1.0 | 1.4 |
| Mn. | 34.1 | 10 | 1.86 | 71.7 | 6.69 | 6.11 | 6.57 | 3.54 | 91.8 | 49.4 | 13.5 | 21.3 | 29.3 |
| $\sigma_{Mn.}$ | | | .06 | 3.4 | | | .56 | .30 | 7.1 | 3.8 | .7 | 1.8 | 4.4 |
| Mn. | 43.3 | 11 | 1.81 | 69.1 | 5.34 | 5.51 | 5.34 | 2.96 | 78.3 | 43.3 | 13.7 | 24.0 | 36.8 |
| $\sigma_{Mn.}$ | | | .04 | 3.0 | | | .32 | .17 | 4.7 | 2.5 | .6 | 1.8 | 4.2 |
| Mn. | 54.8 | 11 | 1.67 | 69.8 | 4.74 | 4.47 | 4.63 | 2.78 | 67.2 | 40.3 | 13.9 | 23.4 | 33.9 |
| $\sigma_{Mn.}$ | | | .05 | 2.8 | | | .21 | .13 | 3.1 | 2.2 | .9 | 1.0 | 1.7 |
| Mn. | 65.4 | 10 | 1.67 | 63.0 | 4.34 | 4.34 | 4.29 | 2.58 | 69.5 | 41.5 | 15.0 | 25.9 | 40.1 |
| $\sigma_{Mn.}$ | | | .06 | 3.2 | | | .28 | .15 | 4.9 | 2.4 | .7 | 1.2 | 3.6 |
| Mn. | 73.3 | 9 | 1.61 | 65.8 | 4.36 | 3.94 | 4.05 | 2.54 | 63.0 | 39.3 | 14.9 | 24.4 | 35.2 |
| $\sigma_{Mn.}$ | | | .05 | 3.6 | | | .25 | .18 | 4.7 | 3.2 | .9 | 1.3 | 1.6 |
| Mn. | 82.0 | 7 | 1.64 | 67.0 | 3.86 | 3.91 | 3.87 | 2.36 | 60.1 | 36.5 | 16.6 | 28.7 | 41.1 |
| $\sigma_{Mn.}$ | | | .07 | 7.5 | | | .39 | .23 | 5.1 | 3.3 | .9 | 2.5 | 4.3 |
| Mn. | 52.5 | 67 | 1.72 | 69.1 | | | 5.08 | 2.94 | 74.2 | 43.0 | 14.1 | 23.6 | 34.5 |
| $\sigma_d$ | 19.1 | | .17 | 12.1 | | | 1.51 | .78 | 18.9 | 9.5 | 2.6 | 5.2 | 19.9 |
| $\sigma_{Mn.}$ | 2.3 | | .02 | 1.5 | | | .18 | .10 | 2.3 | 1.2 | .31 | .6 | 1.3 |

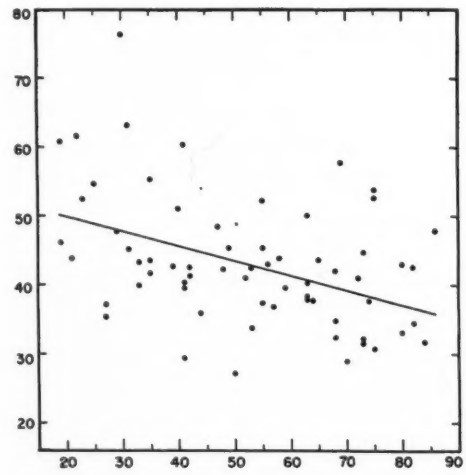


FIG. 3. Stroke output per square meter of surface area versus age. Legend as in figure 1.

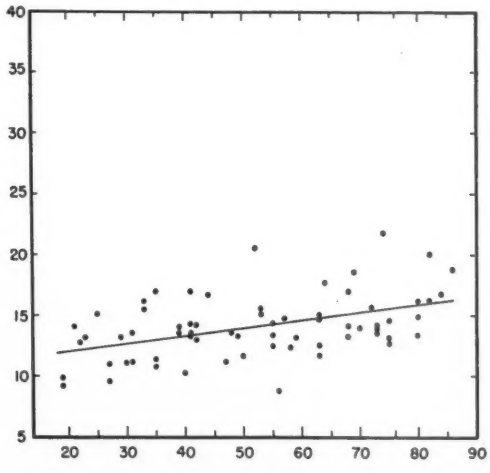


FIG. 4. Circulation appearance time versus age. The time of first detection in the brachial arterial blood of T-1824 after injection of 5 mg. into the opposite antecubital vein under "basal" conditions.

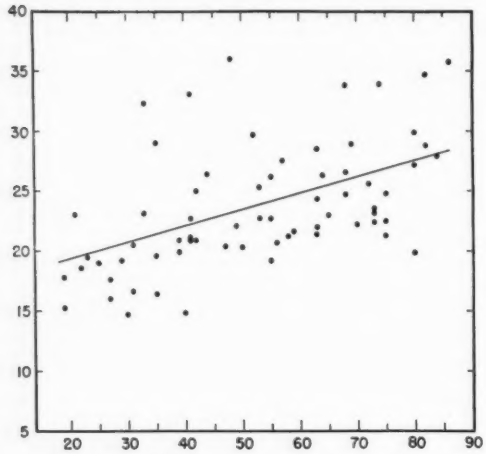


FIG. 5. Circulation time versus age. The mean transit time of T-1824 from antecubital vein to brachial arterial blood after a 5 mg. injection.

Appearance time revealed a small but statistically significant increase with age averaging 0.06 second per year (tables 1, 2, and fig. 4). The mean transit time ($\bar{T}$) averaged 23.7 seconds ($\sigma_d = 5.2$), and increased by an average of 0.14 second per year (tables 1, 2, and fig. 5). There is a trend toward splaying out of the entire time–concentration curve, evidenced best by the increase in passage time with age averaging 0.23 second per year, and supported by the observation that the rate of increase in mean transit time ($\bar{T}$) is twice the rate of the increase in appearance time.

The product of transit time ($\bar{T}$) and cardiac output (C.O.) which is an estimate of central volume (V) showed a slight tendency to decrease with age.

True mean dye transit time was also compared with the mean time of a lag exponential ($\bar{T}_{le}$), a value proposed to estimate mean circulation time.[16] This difference averaged 3.5 seconds, and was highly significant. The effect of this difference increases with age since the $\bar{T} - \bar{T}_{le}$ difference shows an age correlation of 0.48.

Decholin "circulation time" with a mean value of 17.2 seconds, ($\sigma_d = 4.6$) showed an increase approximately twice as great as did appearance time (A.T.), averaging 0.13 second per year. The age increase in Decholin time approximated that for transit time ($\bar{T}$). The correlation coefficient between these two meas-

TABLE 2.—*Statistical Summary of Age Relationships*

| Item | Average 50 Yr. Value* | Standard Deviation of Distribution Per Cent† | Age Correlation Coefficient | Age Regression | | | |
|---|---|---|---|---|---|---|---|
| | | | | Average Per Year‡ | Average Per Cent Per Year‡ | Standard Error Per Cent Per Year | Probability of Chance Effect§ |
| Cardiac output (L./min.) | 5.01 | 32.1 | −.691 | | −1.01 | .130 | <.001 |
| Cardiac index (L./min./M.²) | 2.91 | 28.1 | −.611 | | −.79 | .127 | <.001 |
| Stroke volume (ml./beat) | 72.90 | 29.7 | −.516 | | −.70 | .145 | <.001 |
| Stroke index (ml./beat/M.²) | 42.34 | 25.5 | −.410 | | −.49 | .134 | <.001 |
| Surface area (M.²) | 1.72 | 10.3 | −.419 | | −.22 | .058 | <.001 |
| Heart rate (beats/min.) | 68.7 | 19.7 | −.325 | | −.31 | .110 | <.01 |
| Appearance time (sec.) | 13.9 | 18.5‖ | +.463 | .063 | .45 % | .015 | <.001 |
| Mean transit time (sec.) | 23.4 | 22.1‖ | +.495 | .136 | .58 % | .030 | <.001 |
| Passage time (sec.) | 33.9 | 31.5‖ | +.404 | .230 | .68 % | .0646 | <.001 |
| Central volume (L) | 1.96 | 25.2‖ | −.294 | −.0075 | −.38 % | .0030 | <.02 |
| Mean transit minus theoretical transit time (sec.) | | | +.484 | | | | |
| Mean transit minus decholin time (sec.) | | | +.041 | | | | |

* Based on regression equation.

† $100(\text{antilog } \sigma_{d\log y} - 1.0)$.

‡ Slope of regression equation.

§ Based on $t$ test of ratio of slope of regression equation to its standard error.

‖ Coefficient of variation.

% Slope of linear regression equation expressed as per cent of average 50 year value.

TABLE 3.—*Summary of Published Measurements of Cardiac Index in Relation to Age*

| Author | No. of Subjects | Age Range | Average Decrease in Cardiac Index with Age | | | Method |
|---|---|---|---|---|---|---|
| | | | ml./min./ M.² yr.* | Probability of chance effect† | Per cent of 50 yr. va ıe | |
| Lewis[2] | 103 | 40–101 | 3.6 | >.20 | 0.2 | acetylene |
| Starr, et al.[1] | 78 | 8–76 | 8.4 | >.05 | 0.4 | ethyl iodide |
| Apéria[3] | 111 | 30–70+ | 7.3 | <.001 | 0.4 | acetylene |
| Cournand, et al.[5] | 17 | 21–58 | 26.2 | >.02 | 0.9 | direct Fick |
| Present series | 67 | 19–86 | 24.4 | <.001 | 0.8 | dye dilution |

* Slope of linear regression equation.

† Based upon *t* test of ratio of slope of regression equation to its standard error.

ures (transit time and Decholin time) was 0.395 and the difference between them did not change with age. Thus agewise trends in Decholin time and in the mean transit time for dye ($\bar{T}$) supplied substantially the same information.

## DISCUSSION

Values for cardiac output as here measured show a moderate range among individuals ($\sigma_d = \pm 32$ per cent). Some of this variability* is associated with differences in age, for a sizeable and significant decrease in cardiac output amounting to slightly over 1 per cent of the 50 year value per year, has been demonstrated with age for the subjects constituting this study. Part of the decrease in output is associated with a decrease in body size and part with a decrease in the frequency of the heart beat, but the remainder—about half—is due to reduction in the blood pumped per beat per unit of body size. Cardiac index, i.e., cardiac output per unit of body surface, has been widely used in comparing individuals of divergent size, and is generally useful. A constant of proportionality between output and surface area has not been theoretically or empirically demonstrated, so that other denominators such as body weight[1] justifiably have been used for these comparisons also. Data from this laboratory[21] have shown that while the rate of basal oxygen uptake decreases with age if expressed per square meter of surface area, it does not decline if the data are expressed per liter of body water (represented by antipyrine space). A body water measurement, therefore, may be considered to provide another, and possibly better, estimate of functioning mass than does surface area. Comparison (of two different series of subjects) suggests that the rate of fall in cardiac output is greater than the rate of decrease in antipyrine space. This indicates that the agewise decrease in cardiac output cannot be explained simply as a decrease in functioning body mass. This relationship will be discussed further in the light of additional measures of cardiac and circulatory performance[22]. In table 3, previously published studies, from which statistics in comparable terms have been recalculated, are compared with the current series.† Our findings stand in contrast to the results obtained by Starr and coworkers[1], by Lewis[2] and by Apéria[3] who used indirect gas analysis technics. The present study is in excellent accord with the small series reported by Cournand and his colleagues[5] who used the direct Fick technic and also satisfactorily explains the observations of Smith, and associates[7] in their control series of 10 subjects between 62 and 77 years of age. The presence of three subjects in the age group below 40 years who had cardiac outputs over 9 liters per minute does not detract significantly from the results. In other series, particularly in reports on the direct Fick method, such values are frequently encountered in younger subjects. It is possible, but cannot be established, that the younger subjects were less basal or more apprehensive than the older subjects and conse-

* About half of the variance, which accounts for one third of the standard deviation.

† Data obtained by Olbrich and Woodford-Williams on age changes in dye dilution output have not yet been published in full. (Third Congress, International Association of Gerontology, London, July 19–23, 1954, Symposia and Abstracts, p. 195.)

quently had higher cardiac output and heart rates. The absence of an age trend in the difference between the first and second cardiac output does not bear out this possibility.

The average decrease in cardiac output (C.O.) exceeds the average increase in transit time ($\bar{T}$); thus their product (V) shows a tendency to decrease. This lack of evidence for any increase in central volume in our material is, therefore, no encouragement to the criticism that more of our older subjects had undetected heart disease. In addition the relation between cardiac output and transit time assists in an interpretation of age changes in the kinetics of dye dilution, as follows:

Although the increase in appearance time is most easily and plausibly interpreted as due to a reduction in the velocity of the first dye injected, and/or the fastest moving dyed blood, other factors must be considered. A longer appearance time will also result from (a) a longer traversal pathway, or (b) a slower rise in dye concentration up to the detectable level, without change in the velocity of the earliest arriving dyed blood.

The age increase in transit time was more striking than the increase in appearance time. The increase in transit time would also indicate a decreased mean velocity unless the equivalent traversal path was (a) longer or (c) cross sectional area was greater.

The increase in dye passage time (P.T.) with age, and the increasing spread between appearance time and transit time characterize a greater time dispersion of dyed blood at the sampling site. Since sampling is approximately proportional to blood flow, this reflects a greater final time dispersion in the artery. Such increased splay would be anticipated as a consequence of a decreased velocity, but also would result from (a) an increased length of path (c) a greater cross section, (d) a greater dispersion of individual transit times among multiple paths or (e) a greater mixing in a single path, i.e. more turbulence. It might also be noted that a greater initial dispersion could arise if (f) injection were slower or were made into (g) a venous segment of larger volume or (h) a vessel carrying a greater flow of blood.

The evidence that central volume (V) does not increase indicates that a consideration of (a) and (c), i.e. length and cross sectional area are not paramount. Since only these, besides decreased velocity, are common to an explanation of increases in appearance time (A.T.), transit time ($\bar{T}$), their difference ($\bar{T}$-A.T.) and dye passage time (P.T.), a decrease in mean velocity clearly is implied by the increase in transit time with age.

The prolongation in mean transit time with age averaged 0.6 per cent of the 50 year value per year. Lacking estimates of length and cross-sectional areas, a factor of proportionality cannot be applied to yield linear velocity estimates for individuals or groups. The average prolongation in mean transit time is less than the 1.0 per cent per year average reduction in cardiac output. These values are not independent, since passage time which is related to mean transit time, forms the base of the area from which output is calculated, and the correlation between mean time and cardiac output was $-.495$. Thus the velocity change is consistent with the reduction in blood flow.

Transit time ($\bar{T}$) was observed to differ from the mean time of a lag exponential ($T_{le}$), a proposed estimate of mean time[15, 16] derived from a log slope of the descending limb of dye concentration plus appearance time. A difference between these values ($\bar{T} - \bar{T}_{le}$) becomes a measure of the divergence of the observed time concentration curve from a delayed exponential. Because the construction of the descending limb of the time-concentration curve converts it into an exponential decline, it is obvious that the difference between theory and results represents the contribution of the initial, rising part of the curve, which is not instantaneous. In comparisons of the type we have made, the initial portion of the time concentration curve therefore should not be neglected or assumed to be constant.

The correspondence between the age regressions of Decholin and dye times is reassuring to the clinical interpretation of subjective "circulation times." Our study was not designed to test this point, and, therefore, the circulation time procedure was not highly standardized. The data do not imply that subjective response to Decholin is determined by mean Decholin

transit time at the receptor tissue, but merely indicate a similar regression to that for the dye mean transit time. The similarity between the results of subjective and objective technics fails to provide evidence that increased delay in effector response and/or recognition is a significant factor in the prolongation of Decholin time in our material.

## Conclusions

Cardiac output was determined by an indicator dilution technique in 67 male subjects aged 19 to 86 years selected as being free of relevant disease. The variability of the procedure has been examined, and the estimated error of a single determination was found to be less than 7 per cent.

The cardiac output averaged approximately 5 liters per minute, with individual variation indicated by a 30 per cent standard deviation. Part of this scatter is attributable to age differences. The relationship between cardiac output and age is significant, revealing a reduction of about 1 per cent per year. The reduction in cardiac output in this material is the result of an agewise decrease in stroke index augmented by decreases in body size and heart rate.

Time-concentration curves of indicator were critically analyzed. Corresponding points on these curves tend to occur later in older subjects, while estimated central volume does not increase. This is interpreted as due to a diminution of the velocity of blood flow at least consistent with the observed reduction in volume flow.

## Acknowledgments

We are indebted to Mr. Marvin Yiengst for his construction of the collection rack used and for the excellence of his instruction and advice in blue dye determinations. Mr. William Martin assisted in carrying out many of these determinations. Mrs. Elizabeth Benser and Miss Margaret Christ did much painstaking work on the calculations, tables and manuscript.

## Summario in Interlingua

In 67 masculos—seligite como libere de relevante morbos—le rendimento cardiac esseva determinate per un technica a dilution de indicator. Le variabilitate del procedimento usate esseva investigate con le constatation que le estimate error de un determination unic es infra 7 pro cento. Le rendimento cardiac median esseva circa 5 litros pro minuta con variationes individual indicate per un deviation standard de 30 pro cento. Un parte de iste dispersion es attribuibile a differentias de etate. Le relation inter rendimento cardiac e etate es significative. Illo revela un reduction de circa un pro cento per anno. In le casos studiate per nos le reduction del rendimento cardiac es le resultato de un abassamento del indice del pulso in le curso del avantiamento de etate, augmentate per le reduction del dimensiones corporee e del velocitate del corde.

Esseva executate un analyse critic del curvas del concentration del indicator como function del tempore. Punctos correspondente in iste curvas tende a occurrer plus tarde in le caso de individuos a etates plus avantiate, sed le volumine central non se augmenta. Isto es interpretate como un effecto del diminution del velocitate del fluxo sanguinee a un grado al minus correspondente al observate reduction del fluxo de volumine.

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# The Relation of Age to Certain Measures of Performance of the Heart and the Circulation

By Milton Landowne, M.D., Martin Brandfonbrener, M.D. and Nathan W. Shock, Ph.D.

The resting cardiac output measurements presented in the preceding article are analyzed in relation to intra-arterial pressure to provide estimates of peripheral circulatory state and of central cardiac performance. The calculated agewise increase in net vascular resistance which is responsible for the decrease in perfusion, indicates that circulatory attrition with age, on the average, outstrips the expected reduction in basal metabolism of the individual. Despite this lessened peripheral requirement, one may adduce evidences for a trend toward diminished cardiac reserve with age even in these subjects who revealed no clinical cardiac abnormality. The feasibility of predicting an individual's cardiac output from his blood pressure is commented upon.

THE resting cardiac output represents one of the important measures of *cardiac* performance, and this information also forms a basis for estimates of the performance of the *circulation*. Observations of systolic and diastolic blood pressure[1] are interpreted to indicate that an increase in all parameters of pressure may occur with age. Since resting cardiac work considers both the contributions of pressure and of volume flow, an apparent increase in mean pressure during systole in the absence of reciprocal change in output indicates an increase in the resting external work of the heart. Unless loading pressure is altered, this would indicate a change in tension-length relationships and in the contractile performance of the heart as a muscle; or alternatively, a decrease in nonmeasured work. In this manner the evaluation of cardiac performance (in terms of work) involves a consideration of the interrelationship of output and pressure.

It has been demonstrated, or indicated to be likely, that regional increases in the renal,[2] cerebral,[3] and extremity resistances[4] occur with age. This would reflect either an increase in total resistance of the greater circulation, a significant redistribution of this resistance or both. An increase in mean arterial pressure, in association with a decrease in cardiac output would indicate an increase in total resistance and thus the interrelationship of output and pressure provides for an evaluation of peripheral circulatory performance.

Some idea of central circulatory performance may also be ventured. The rate of fall of arterial pressure during diastole will vary inversely with arterial distensibility if the peripheral resistance is kept constant. Estimates of resistance thus allow an interpretation of rate of diastolic pressure fall to be made in terms of central arterial distensibility.

The foregoing relationships have provided a basis for examining the implications of the agewise alterations in cardiac output which we have reported.[5]

## Methods

The 67 subjects providing cardiac output data are described in the previous report.[5] In each of these subjects a record of heart rate and brachial intra-arterial pressure was obtained through a Statham P23A strain gage and a Sanborn amplifier and direct writing oscillograph immediately before the determination of cardiac output. In 53 subjects, a second determination of blood pressure, heart rate and cardiac output was made 10 minutes after the completion of the first. The records obtained were analyzed as follows (fig. 1).

*Heart Rate* in beats per minute was measured as the reciprocal of the average cycle length of 10 consecutive brachial arterial pressure pulses (in three subjects, five pulses were used) recorded just before each determination of cardiac output.

The *duration of systole* ($t_s$) in seconds was esti-

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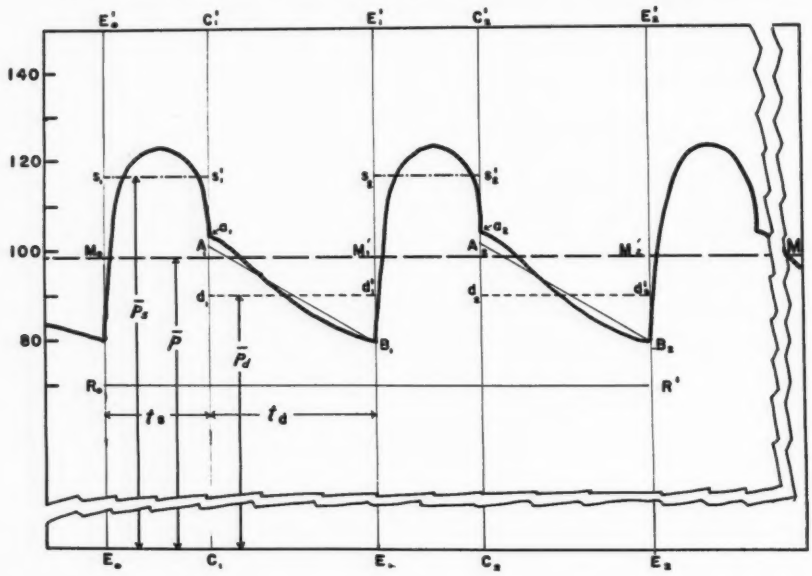


FIG. 1. Derivation of estimates of pressure and time from recorded curves, (ordinate mm.Hg, abscissa time).

Mean pressure ($\bar{p}$) corresponds to the height of line MM, and is obtained by dividing the planimetrically measured area under 10 consecutive beats by the time interval. Systolic interval, mean systolic pressure ($\bar{p}_s$), mean diastolic pressure ($\bar{p}_d$), and relative rate of diastolic pressure fall, are estimated for each of two of these 10 beats as shown: Vertical lines $CC'$ are drawn through ($a$) the point of most rapid change in decreasing pressure, marking estimated commencement of diastole; and $EE'$ through ($B$), the estimated end of diastole. This divides the cycle length ($t_c$) into a systolic ($t_s$) and a diastolic ($t_d$) period.

The total pressure area under the curve per beat is approximately equal to the average pressure area for the beat, $\bar{p} \times (t_s + t_d)$, or rectangle $M_0M_1E_1E_0$.

From $B$, line $AB$ is drawn to intersect $CC'$ at $A$, selecting $A$ so that the area ($ABEC$) under line $AB$ is equal to the diastolic pressure area $aBEC$ under curve $aB$. The discrepancy between ($a$) and $A$ is exaggerated, in order to illustrate the construction. Line $dd'$ is drawn so that $dC = \frac{AC + BE}{2}$, and the area of rectangle $dd'EC$ is therefore equal to the diastolic pressure area $aBEC$. The width of this rectangle is the diastolic period $t_d$ and the height is the estimated mean diastolic pressure $\bar{p}_d$, corresponding to the level of line $dd'$.

The systolic pressure area is obtained as the difference between the mean pressure area $\bar{p} \times (t_s + t_d)$ and the diastolic pressure area $\bar{p}_d t_d$, and may be represented as rectangle $S_1S_1'C_1E_0 = \bar{p}_s t_s = \bar{p}t_c - \bar{p}_d t_d$ with width $= t_s$ and height $=$ estimated mean systolic pressure, $\bar{p}_s$. A measure of the average relative rate of diastolic pressure fall is obtained as $\frac{\Delta_d}{\bar{p}_d t_d}$, where $\Delta_d$ = the fall in pressure during diastole or $AC - BE$.

mated for each of two representative pressure pulses out of 10 pulses mentioned above. The length of systole was approximated as the interval from the beginning of increase in brachial pressure to the point of most rapid change in the shape of the pressure curve after the systolic peak occurred. The total cycle length ($t_c$) for each of these pulses was thus partitioned into a systolic duration ($t_s$) and a diastolic duration ($t_d$).

*Mean Brachial Arterial Pressure* ($\bar{p}$) in millimeters of mercury was measured as the planimetric average of the brachial arterial pressure pulses (10 consecutive beats in all but two subjects). The brachial mean pressure is employed in the resistance formula as an estimate of the mean pressure at the root of the aorta upon the unproved assumption that the difference between mean pressures at the two locations would be small and would not show

any material agewise change. *Maximum systolic pressure* ($p_{max}$) and *minimal diastolic pressure* ($p_{min}$) represent the conventional systolic and diastolic pressures, and were, respectively, the visual averages of 10 consecutive systolic pressure peaks and diastolic minima in millimeters of mercury.

The *mean pressure during systole* ($\bar{p}_s$) in millimeters of mercury, was obtained for each of the two beats used to estimate systolic duration by dividing the pressure area during systole by the systolic duration, after the systolic pressure area was estimated by subtracting the diastolic pressure area from the total pressure area per beat. The total pressure area per beat was taken as the product of the mean pressure for 10 beats ($\bar{p}$) times the cycle length ($t_c$) of the appropriate beat. The diastolic pressure area ($\bar{p}_d t_d$) was estimated by extending a diagonal line from the pressure curve at the end of the diastolic period backwards along the diastolic pressure fall to the ordinate representing the end of the systolic period, so that approximately equal areas were included above and below the diagonal line by the pressure record. The area of the trapezoidal figure thus produced was taken as the diastolic pressure area and could be readily calculated as the product of the base which was the diastolic period ($t_d$), and the average of the ordinates corresponding to the beginning and the end of this period. Thus $\bar{p}_s = \frac{\bar{p}t_c - \bar{p}_d t_d}{t_s}$. A two-beat average was obtained to correspond with each determination of cardiac output.

*Cardiac Work* ($W$) (left ventricular stroke work) was estimated as the product of stroke volume ($S.V.$) and mean pressure during systole, and converted into conventional units $\left(W = 14.3\ \bar{p}_s \times S.V. \frac{gram\text{-}meters}{beat}\right)$. This definition arbitrarily defines the "useful" cardiac work[17] neglecting the velocity component at rest as inconsequential. *Cardiac power* ($P$) (left ventricular power) or average work rate during systole, was estimated by the ratio of work to the length of systole and is readily expressed in watts. $\left(P = 1.40 \times 10^{-4} \frac{\bar{p}_s \times SV}{t_s}\ watts\right)$. It is recognized that estimations of systolic intervals from brachial pressure records cannot be considered accurate. There was, however, no age difference in the ratio of systolic duration thus determined to total cycle length $\left(\frac{t_s}{t_c}\right)$. An error in inferring the mean systolic pressure at the root of the aorta from an estimate of brachial mean systolic pressure is of more concern since an agewise difference in any discrepancy between these pressures may also arise due to differences in the propagation characteristics of the pressure wave. Furthermore, the calculation of pressure-volume work should consider the integral of the product of instantaneous pressure and instantaneous volume, for which we are substituting mean values. Despite such acknowledged inaccuracy and limitations, the estimates made appear preferable to the simple use of estimated mean pressure for the entire cardiac cycle, because they are theoretically more appropriate and generally tend to underestimate rather than overestimate the age differences here reported.

*Resistance* ($R$) (total peripheral resistance of the greater circulation) was estimated as the ratio of mean arterial pressure to cardiac output without correction for non-Newtonian flow, for end-diastolic left ventricular pressure or for estimated differences in blood viscosity.

$$\left(R = \frac{\bar{p}}{C.O.} \frac{mm.Hg.min.}{liters}\right).$$

*Central Elasticity* ($E$). An estimate of volume elasticity was defined as the product of total resistance of the greater circulation and the fractional rate of fall in pressure during diastole: $\left(E = 80 \frac{R\Delta d}{t_d \bar{p}_d} \cdot \frac{dynes/cm.^2}{cm.^3}\right)$ (Apéria[6], equation $14_3$). The diastolic relative pressure fall may be expressed for an exponential decline in pressure during diastole as $\log\left(\frac{\text{end systolic pressure}}{\text{end diastolic pressure}}\right)$; and where diastolic pressure decline is approximately linear the corresponding approximation is $\frac{\Delta_d}{\bar{p}_d}$, or diastolic pressure fall expressed as a fraction of mean diastolic pressure. $\Delta_d$ and $\bar{p}_d$ (fig. 1) were obtained as the averages of two beats for each determination of cardiac output ($C.O.$) and mean pressure ($\bar{p}$), providing two estimates of $E$ in the 53 subjects where two determinations of cardiac output were performed. If pulse pressure ($p_{max} - p_{min}$) is proportional to $\frac{\bar{p}}{t_d} \frac{\Delta_d}{\bar{p}_d}$, the expression for $E$ could be further simplified to $\frac{K(pulse\ pressure)}{C.O.}$. This was examined by comparing $E' = \frac{p_{max} - p_{min}}{C.O.}$ and $E$.

For convenience and consistency in tabular and textual presentation of results the statistics of simple linear regressions of the logarithm of values against age have been generally used, but without implying any particular mode of actual regression.

## Results

*Blood Pressure.* The upper clinical limits of blood pressure in these subjects was fixed by

TABLE 1.—*Summary of Results by Decades*

| | Age | $n$ | Surface Area, M.² | Max. (Systolic) Pressure mm. Hg ($p_{max}$) | Min. (Diastolic) Pressure mm. Hg ($p_{min}$) | Planimetric Mean Pressure mm.Hg ($\bar{p}$) | Systolic Mean Pressure mm. Hg ($\bar{p}_s$) | Stroke "Work" Gm.m./beat ($W$) | Stroke "Power" Watts ($P$) | "Resistance" mm. Hg L./min. ($R$) | Heart Size, Length, cm. | Heart Size, Breadth, cm. | % of Predicted Cardiac Area | "Elasticity" dynes/cm.² / cm.² ($E$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean | 23.6 | 9 | 1.75 | 115.3 | 65.1 | 85.3 | 101 | 125 | 5.23 | 13.7 | 12.7 | 10.4 | 87.3 | 593 |
| $\sigma_{Mn.}$ | | | .04 | 2.4 | 2.1 | 2.2 | 2.8 | 10.9 | .41 | .9 | .4 | .2 | 4.0 | 43 |
| Mean | 34.1 | 10 | 1.86 | 119.2 | 63.7 | 87.8 | 106 | 141 | 5.42 | 14.0 | 13.4 | 10.7 | 90.4 | 678 |
| $\sigma_{Mn.}$ | | | .06 | 4.2 | 2.0 | 2.9 | 3.9 | 14.2 | 5.1 | .9 | .3 | .3 | 3.8 | 52 |
| Mean | 43.3 | 11 | 1.81 | 124.8 | 68.7 | 93.0 | 110 | 122 | 4.31 | 18.0 | 13.4 | 10.5 | 93.1 | 856 |
| $\sigma_{Mn.}$ | | | .04 | 3.6 | 2.7 | 2.8 | 3.7 | 7.4 | .27 | 1.1 | .5 | .2 | 4.4 | 49 |
| Mean | 54.8 | 11 | 1.67 | 132.3 | 70.0 | 97.5 | 116 | 112 | 3.89 | 21.3 | 13.5 | 10.4 | 97.7 | 1106 |
| $\sigma_{Mn.}$ | | | .05 | 8.5 | 3.5 | 5.5 | 7.7 | 9.4 | .36 | 1.3 | .3 | .2 | 3.3 | 73 |
| Mean | 65.4 | 10 | 1.67 | 137.4 | 61.0 | 90.5 | 113 | 114 | 3.64 | 21.5 | 13.8 | 10.3 | 100.4 | 1150 |
| $\sigma_{Mn.}$ | | | .06 | 3.9 | 2.6 | 2.9 | 4.0 | 10.8 | .32 | .9 | .2 | .1 | 2.3 | 101 |
| Mean | 73.3 | 9 | 1.61 | 134.0 | 62.1 | 90.1 | 112 | 101 | 3.30 | 22.9 | 13.5 | 10.5 | 102.7 | 1288 |
| $\sigma_{Mn.}$ | | | .05 | 5.8 | 3.0 | 4.3 | 5.0 | 8.4 | .27 | 1.8 | .3 | .2 | 3.3 | 115 |
| Mean | 82.0 | 7 | 1.64 | 144.1 | 59.3 | 92.0 | 115 | 101 | 3.62 | 25.5 | 13.7 | 10.7 | 103.1 | 1687 |
| $\sigma_{Mn.}$ | | | .07 | 6.3 | 1.7 | 3.6 | 5.4 | 11.1 | .48 | 3.3 | .4 | .4 | 4.7 | 353 |
| Mean | 52.5 | 67 | 1.72 | 129.0 | 64.7 | 91.1 | 110 | 117 | 4.23 | 19.3 | 13.4 | 10.5 | 96.1 | 1023 |
| $\sigma_d$ | 19.1 | | .17 | 18.4 | 8.8 | 11.6 | 15.5 | 33.5 | 1.36 | 5.9 | 1.1 | .7 | 12.3 | 482 |
| $\sigma_{Mn.}$ | 2.3 | | .02 | 2.3 | 1.1 | 1.4 | 1.9 | 4.1 | .17 | 0.7 | .1 | .1 | 1.5 | 58 |

reason of an exclusion criterion used in their selection. The intra-arterial records obtained revealed that despite the limitation, as may be seen in table 1,* there was a gradual increase in the average maximal (systolic) blood pressure from 115 mm. Hg in the youngest age decade to 144 mm. Hg in the oldest. The minimal (diastolic) pressure remained fairly constant and the true mean pressure showed insignificant changes with age. These peak and minimal values were reflected respectively in the computed average pressure during the systolic interval and the average pressure during the diastolic interval but the age change in mean systolic pressure ($\bar{p}_s$) was not as striking as was the change in peak pressure ($p_{max}$).

*Cardiac Rate.* The mean value of heart rate per decade appears to decline with age and the relationship between these two is of borderline significance, (tables 1 and 2[5]). There was no age change in the fraction of the cycle occupied by estimated systole. This fraction averaged 0.316 ($\sigma_d = \pm.036$); its coefficient of variability was relatively small (11 per cent). There was thus an age increase in the estimated systolic duration as well as in the total cycle length.

Estimates of *left ventricular work* indicate that with age the decline of cardiac output more than balances the increase in systolic blood pressure. A linear regression for log work vs. age has been employed as a convenient representation of results. The regression coefficient was significant at the 1 per cent level. The net decrease in stroke work per year averaged almost 0.5 per cent (tables 1 and 2). The expression for *power*, namely the ratio of heart work per beat to systolic duration, showed a more striking decline with age, decreasing per year by an average of 0.9 per cent (tables 1 and 2 and fig. 2). In other words, despite the increase in esti-

* At the request of the editor, the individual data have been omitted from table 1. These data will be furnished by the authors on request as long as copies are available. They have also been deposited with the Photoduplication Service, Library of Congress, Washington 25, D. C., as document no. 4675

TABLE 2.—*Statistical Summary of Age Relationships*

| Item | Average 50 yr. Value* | Standard Deviation of Distribution, Per Cent† | Age Correlation Coefficient | Age Regression | | |
|---|---|---|---|---|---|---|
| | | | | Average Per cent per year‡ | Standard Error per cent per year | Probability of chance effect§ |
| Resistance (mm.Hg min./liters) | 18.0 | 35.1 | +.708 | 1.11 | .138 | <.001 |
| Stroke Work (gm.M./beat) | 113.2 | 34.4 | −.315 | −.49 | .182 | <.01 |
| Power (watts) | 4.13 | 37.6 | −.546 | −.91 | .174 | <.001 |
| Central elasticity (dynes/cm.²/cm.³) | 903 | 49.1 | +.755 | 1.58 | .170 | <.001 |
| Mean blood pressure (mm.Hg) | 90.1 | 13.3 | +.160 | .10 | .079 | >.1 |
| Mean systolic pressure (mm.Hg) | 108.8 | 14.9 | +.298 | .22 | .086 | <.1 |
| Peak systolic pressure (mm.Hg) | 127.8 | 14.2‖ | +.500 | .38 # | .081 | <.001 |
| Systolic duration (sec.) | | | .489 | | | |

* Based on regression equation.
† 100 (antilog $\sigma_{d_{\log y}} - 1.0$).
‡ Slope of regression equation.
§ Based on "t" test of ratio of slope of regression equation to its standard error.
‖ Coefficient of variation.
# Slope of linear regression equation expressed as per cent of average 50 year value.

mated duration of systole, there was a decrease in the recorded work performance of the left ventricle so that the computed rate of doing work decreased. It is worthy of note that a slower heart rate occurred in the presence of a reduced stroke volume; the systolic fraction of heart rate remaining the same, so that neither absolute nor relative systole were shortened.

Estimated *resistance* of the greater circulation per subject (table 1, 2), or relative to surface area (fig. 3), showed a rapid increase until the sixth decade, and an overall highly significant increase with age. In our material this is almost entirely attributable to the reduction in flow,

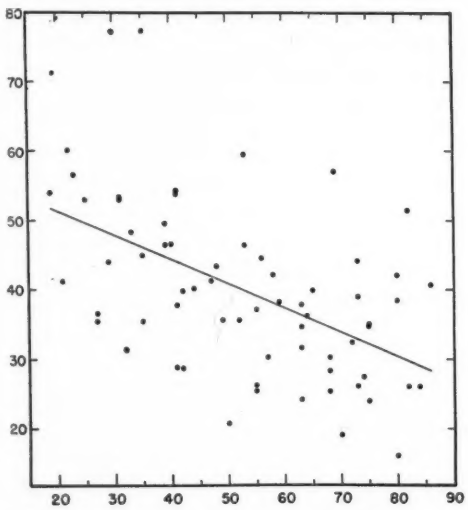


FIG. 2. Estimated left ventricular stroke power plotted in relation to age for 67 males under 'basal' conditions. See text for derivation of work and power estimates. The ordinate scale in this figure should be multiplied by 1.05. In this and succeeding figures ordinate scales are approximately proportional. In figures 2 and 3, the line represents the simple linear regression for the data.

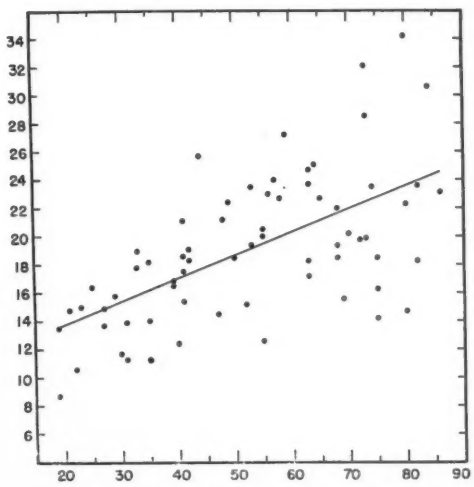


FIG. 3. Estimated total peripheral resistance of the greater circulation in relation to surface area, vs age. Legend as in figure 2. The data in tables 1 and 2 refer to total resistance per subject.

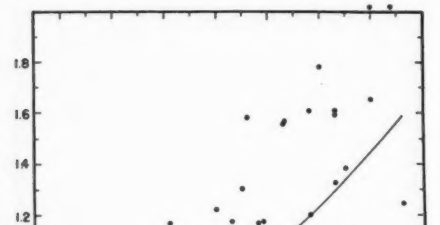


FIG. 4. Estimated central elasticity ($E$) vs age. Legend as in figure 2, the line indicates the simple linear regression of log $E$ on age.

the correlation and regression matching that for cardiac output closely.

*Central Elasticity* ($E$). This estimate varied from 446 to 3567 dynes per cm.$^2$ per cm.$^3$, increasing with age by an average of 1.58 per cent per year (tables 1 and 2 and fig. 4). The correlation between log $E$ and age was the highest of any correlation tested for either $E$ or age ($r = 0.76$) with the exception of log ($E \cdot t_d$) which showed a correlation of 0.81 with age, reflecting the effect of the age change in heart rate. The standard error of estimate of $E$ from the regression of log $E$ with age was 30 per cent. Replicate calculations of $E$ in 53 subjects furnish an estimate of the replication error of a single calculation as 12 per cent. The ratio of pulse pressure to stroke volume, or $E'$, provided essentially the same information, for this averaged 0.94 $E(\sigma_d = \pm.14)$. $E'$ was also highly age correlated ($r = 0.67$) and the standard error of estimate of $E'$ from its age regression was 35 per cent of the mean value.

## DISCUSSION

*Blood pressure.* Planimetric mean pressure ($\bar{p}$) was measured because of the possibility that approximations of mean pressure would introduce an agewise bias. Mean pressure revealed little agewise change, while there was a significant increase in maximum systolic pressure ($p_{max}$) and in the arithmetic mean of maximum systolic pressure ($p_{max}$) and minimum diastolic pressure ($p_{min}$). The difference between true mean and arithmetic mean averaged only 6 mm. Hg but showed a significant increase with age. Our estimates of resistance change are thus not overdrawn. Lacking evidence of the accuracy of our estimates of systolic duration, the age increase in mean pressure cannot be critically interpreted. It is less striking than is the increase in maximum systolic pressure, and we have no reason to consider that the use of brachial for aortic records introduced an agewise bias in the estimates presented.

*Cardiac output and peripheral resistance.* The average rate of decline in cardiac output with age observed by us[5] is conveniently expressed as 1.01 ± 0.13 per cent per year, and is almost entirely in relation to an increase in peripheral resistance which averages 1.11 ± .14 per cent a year. These changes are greater than the calculated rates of average decrease with age for total oxygen consumption (0.53 ± .05*, or 0.46 ± .09† per cent per year), total carbon dioxide production (0.53 ± .07* per cent per year), calories per square meter per hour (0.40 ± .05* per cent per year), or estimated intracellular fluid volume (0.58 ± .12† per cent per year) reported for similar but less rigidly selected groups of subjects.

Considering these four items as general indices of the reduction in metabolically active tissue, the demonstration of a disproportionately greater reduction in perfusion would have as its corollary an average increase in oxygen and carbon dioxide extraction, i.e. in A-V

* Representing the average regressions and their standard errors, expressed as per cent of the corresponding 50 year values, in the following statistics which were obtained from the data and statistics of Yiengst and Shock[7]:

*$O_2$ uptake, ml./min.* = 212 − (1.12 ± 0.11) $a$
*$CO_2$ production ml./min.* = 172 − (0.92 ± 0.12) $a$
*Calories/hr./m.$^2$* = 34.65 − (0.14 ± 0.02) $a$
where $a$ = age minus 50 years

† Representing the average rate of change per year, based upon the following regression statistics calculated from the data of Shock and co-workers[8]:

*$O_2$ uptake, ml./min.* = $195\ e^{(-.0046 \pm .0009)a}$
*Antipyrine minus thiocyanate "space", liters* = $16.45\ e^{(-.0058 \pm .0012)a}$
where $a$ = age minus 50 years

difference. Although Lewis[10] found no significant change, increased A-V differences have been noted in age studies by Apéria[9] and by Cournand and associates,[11] and the larger average removal of oxygen and acquisition of carbon dioxide per unit of blood flowing thus serves to compensate for a reduction in total perfusion which is relatively greater than the reduction in total cellular activity. It is thus probable that the estimated average increase in vascular resistance is primary to the average reduction in total cellular activity. If these occurred pari passu, or if cellular alteration were to be considered primary to reduction in circulation,[12] it would not be likely that the decrease in perfusion would exceed evidences of reduction in cellular activity. If impaired diffusion or transport from blood to tissues were a primary factor in the reduction in cellular gas exchange rate, A-V differences would not increase. The evidence for primary vascular alteration is intended to apply to the total circulation generally, for in any specific circulatory region circumstances may be quite different.

A comparison of the changes in renal blood flow[13] with these changes in total blood flow, reveals that the average reduction per year in renal perfusion represents more than half of the total average reduction in cardiac output, although the kidneys in a young adult receive less than one fourth of the total flow. The increase in renal resistance with age[14] is therefore more striking than is the increase in average resistance of the remaining organs perfused by the greater circulation.* Moreover the relatively low renal A-V oxygen difference reflects a high perfusion-oxygen uptake ratio in comparison to the lumped remainder of the circulation. The renal perfusion-mass ratio may also be inferred to be high. Consequently, regardless of any agewise decrease in renal oxygen uptake or mass, the changes in renal resistance contribute in good measure to the overall disproportionality we have deduced between decreased perfusion and diminished oxygen uptake. Not only each circulatory segment but each metabolite may contribute to the overall picture in a different fashion.

*Work, power, cardiac size.* The increase in the duration of systole in the face of a decrease in cardiac work describes a change in the power developed by the heart and consequently, under these circumstances, in the performance curve of the myocardium. This is lent emphasis by the observation that cardiac size in the older individual does not decrease.

Although the subjects in these studies are defined as "normal," i.e. free from clinically relevant cardiac disease, it may well be argued that the observations herein reported are due to an increased agewise incidence and severity of diseases of the heart not detectable by the methods of evaluation used. No objection will be taken to such an argument since no primary standard is available to us by which we can ascertain freedom from coronary artery disease, and we are aware of the age incidence of morphologic involvement of the coronary arteries by atherosclerosis.[16] The decrease in cardiac output and work observed with age ought not to be considered as evidence that the older subjects had subclinical heart disease since in compensated heart disease normal or even high values may be obtained.[17]† It appears to most subjects and free of any great agewise bias. Even then, our results would imply operative differences and not necessarily differences

* Nonrenal flow and resistance estimates have been made by combining the present data and the data on renal function of Davies and Shock,[13] and suggest an average change of approximately 0.9 per cent per year.

† Starr and associates,[15] applying Starling's Law to clinical evaluation, expounded a relation of basal left ventricular work to heart size, and used this as a measure of the function of the heart. In our material, estimated cardiac size did not vary widely (coefficient of variation was 13 per cent), and evidenced no systematic alteration with age (table 1). Within this range of heart size, there was no demonstrably significant relation between stroke work and cardiac area ($r = .11$). Absolute values of our series cannot be compared with the 78 subjects with 'normal circulations' studied by Starr and coworkers, because different and noncomparable technics were employed. The ethyl iodide method of estimating cardiac output, and the use of mean pressure, yield average work estimates which are almost 40 per cent less than ours, while our estimates of cardiac size are not as accurate as the orthodiagraphic method. The "standard deviation about regression" of stroke work in Starr's series of 78 subjects with normal circulations was

more likely that the decrement in cardiac output is related in part at least to alterations in the circulatory requirements of older people at rest and in part to an alteration in performance of the myocardium itself.

Although estimates of left ventricular end-diastolic pressure are not available, an agewise decrease in end-diastolic pressure is unlikely unless right ventricular functional decrease far exceeded left. Antecubital venous pressure showed no significant age change in our subjects and heart size did not decrease; in either event, the increased period of diastolic filling per stroke associated with a decreased cardiac output and a decrease in cardiac work indicates an unfavorable change in the fundamental relationship of diastolic volume and work. We picture, therefore, in the older individual, a heart which is operating on a different performance curve and working closer toward the limit of its performance.

It is noteworthy that although the volume delivered by the heart lessens with age, the work shows a smaller decline; that is, a greater proportion of available energy is spent overcoming friction and developing pressure, and there is a reduction in the energy which is available for propelling blood. The surviving isolated dog heart performs more efficiently when work is increased by increasing output then when work is increased by increasing pressure.[17] A calculated decrease in left ventricular work which is achieved as a net result of a decrease in output and a slight increase in pressure may therefore not represent a more favorable operating circumstance. It may be worth emphasizing that the work calculated here represents the useful work largely by definition, and that the total work output of the older heart may not actually decline, but simply a smaller fraction of this work may be rendered effective. The work done in imparting a velocity to blood is inconsequential under resting conditions and certainly does not increase with age, but numerous other possibilities exist for the transfer and dissipation of energy ultimately derived from myocardial contraction.[17] If the calculated efficiency of the heart tends to be reduced by these alterations, either a greater proportion of energy liberated is not being utilized for work in propelling blood, or there is a lesser liberation of energy for the quantity of substrate consumed. Neither alternative can be assumed without definite information as to the energy cost of work, because the greater diastolic stretch imposed by a longer diastolic period normally operates to increase efficiency and will tend to restore over-all performance. This compensatory mechanism would be one possible explanation of the reduction in heart rate which is here observed, and has elsewhere been reported to occur with age.[18]

It does appear of substantial importance to reiterate, that the work output of the heart is accomplished over a longer period of time and this can be expressed by the statement that the power performance of the heart is reduced in the older individual at rest.

*Elasticity.* Our estimates of relative central elasticity imply an almost three-fold change between 20 and 80 years of age. The reproducibility and striking age correlation are more impressive in view of the fact that standard clinical instrumentation was employed with arbitrary use of approximation to theory; and that compilation was free of detectable age bias. Despite the high age correlation we have found for this estimate, it does not yet provide a satisfactory means of predicting the individual cardiac output from recorded blood pressure curves, since the standard error of predicted $E$ or $E'$ was over 30 per cent in our subjects, and any uncertainty of elasticity enters proportionately into the calculation of cardiac output from $E\left(CO = \frac{80\ \bar{p}\Delta d}{E\ \bar{p}_d t_d}\right)$ or $E'\left(\mathrm{CO} = \frac{p_{\max} - p_{\min}}{E' t_c}\right)$. We have primarily considered these estimates of elasticity to indicate certain inter-relations of time, flow and pressure. They can only be construed as denoting age differences in volume distensibility if the approximation formula is equally appropriate

about 30 per cent of the mean stroke work. The standard deviation of the distribution in our series is no greater than this, indicating that our "normal" subjects show no greater dispersion in this estimate of cardiac function (stroke work relative to heart size) than did the younger series of Starr and his colleagues.

in tissue moduli, since estimates of vascular dimensions are not included.

## Conclusions

(1) For a selected group of subjects in whom cardiac output was measured, the increase in mean brachial pressure with age was not significant, although systolic pressure increased.

(2) The ratio of pressure to flow, a measure of the total vascular resistance of the greater circulation, increased with age. The reduction in tissue perfusion or the increase in resistance are significant, relative to estimates of body size and by comparison are greater than are the reductions which have been noted in oxygen uptake, carbon dioxide production or "intracellular water." These are evidences of an average reduction in the generosity of cellular perfusion.

(3) From the central standpoint these observations reflect a decrease in "useful" cardiac work, since the calculated pressure component increase is not comparable with the decrease in output. The estimated duration of systole does not shorten, but increases, resulting in a decrease in calculated rate of work performance or power. The increase in the pressure component of work, the decrease in power and an increase in relative heart size, are evidences of a reduction in the effective reserve of the left heart as a muscle pump.

(4) Estimates of central elasticity are developed, these are highly age-correlated.

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## Summario in Interlingua

1. In un gruppo de subjectos seligite le rendimento cardiac esseva mesurate. Le augmento del pression brachial median con avantiamento de etate non esseva significative ben que le pression systolic se augmentava.

2. Le proportion de pression e fluxo—un mesura del resistentia vascular total in le circulation major—se augmentava con avantiamento de etate. Le reduction del perfusion texital e le augmento del resistentia in relation a estimationes del dimensiones corporee es significative. Illos es comparativemente plus grande que le reductiones que ha essite notate in le absorption de oxygeno, le production de dioxydo de carbon, o le "aqua intracellular." Iste datos es indicative de un reduction median del abundantia e perfusion cellular.

3. Ab le puncto de vista central iste observationes reflecte un reduction del "utile" labor del corde, proque le calculate augmento del componente de pression non es comparabile con le reduction del rendimento. Le estimate duration del systole non se reduce; illo accresce, lo que resulta in un reduction del calculate ratas de activitate o de potentia. Le augmento del componente pressional del labor, le reduction del potentia, e le augmento del dimensiones relative del corde es indicationes de un reduction del reservas effective del corde como pumpa muscular.

4. Esseva disveloppate estimationes del elasticitate central. Istos indica un alte grado de correlation con le etate del subjecto.

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# Dynamic Comparison of Current Ballistocardiographic Methods

## Part I: Artefacts in the Dynamically Simple Ballistocardiographic Methods

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This paper will be presented in three parts, appearing in successive issues of Circulation. In Part I certain force artefacts arising from the method of supporting the body, are compared with the "true" cardiovascular forces. This is done for the methods of Burger, v. Wittern, Dock-Taubman, Smith and Walker. These are approximately *single-mass* systems in which platform effects prove negligible or absent; so that at the lower ballistocardiographic frequencies, the internal driving forces on the body are opposed by relatively simple constraints. At this stage also, we will examine the complementary meanings of displacement, velocity and acceleration records. The same record (e.g. "body displacement") can have various physical meanings, depending on what aspect of cardiovascular dynamics the reader wishes to refer to. If, however, resonance occurs in the spectrum (direct-body methods), it is shown why no clear physical meaning applies to any of the records: displacement, velocity, or acceleration.

In Part II we show experimentally that a similar analysis in terms of *two masses* applies fairly well to the bed methods. This analysis shows how the platforms of Starr, Nickerson, Burger and v. Wittern affect the errors over a wider BCG frequency band. Principles and methods for minimizing these errors will be examined.

In Part III we examine the validity of the standard assumptions of ballistocardiography, employed in Parts I and II. Using ballistocardiographic records taken with and without beds, and subtracting the effects of the supports under the usual assumption, we show that mechanical errors still remain. Constraints to ground as stiff as the direct-body and Starr supports seem to excite more errors of body complexity than do the softer supports of Nickerson and Burger or v. Wittern, beyond the obvious distortions from resonance. Conclusions are drawn about the direction of progress toward more informative and reliable BCG records.

THE aim of ballistocardiography is to deduce the dynamics (forces, momenta and motions) of particular cardiovascular mechanisms (heart, great vessels) from the recorded motion of the body.[1, 2] The composite or vector accelerations of the rapidly varying cardiovascular masses are not seen directly, but through a complex transmitting system: the body.

Such deductions rest on certain assumptions generally accepted, but not always stated. The body is considered a lumped or centralized mass, moving as a whole. This assumption is accepted in Parts I and II but its errors will be illustrated, and are analysed in Part III. Secondly, the cardiovascular forces, momenta, moments,[A1*] energies and impulses are assumed localized in a definite configuration (rather than distributed continuously); however, the vector sums change continually in magnitude, direction and location. This assumption enables one to write simple equations in which forces are added. (The alternative, continuous distributions, requires the forbidding analytical apparatus of partial differential equations.) Thirdly, it is assumed that these forces produce body motions by acting directly on a body mass resting on supports by couplings which are passive and linear (no power-law terms): i.e., the cardiovascular forces are not assumed to act on the body mass via elastic or viscous tissue.[5] In other words, the body mass and acceleration

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* Superscript numbers with "A" refer to sections of the appendix.

(in the simplest case) are assumed to give the cardiovascular force directly.

Since these curious assumptions are implicit in the previous analyses of the ballistocardiogram (BCG), and ballistocardiographic interpretation depends on them, their utility and validity will be of interest.

Recording of the ballistocardiogram is intrinsically more complicated than the electrocardiogram. In the latter, extraneous electrical forces and grounds are easily excluded. In a mechanical system, however, the *earth* exerts inescapable forces on all parts of the body: gravity, the shear and compressive forces of supports, and the inertial reference of mass reactions when accelerated. In most cases these forces are out of phase with their effects, a further complexity negligible in electrocardiography. It is not surprising to find that the various ballistocardiographic methods differ mainly in how they treat these earth-forces, exerted through various supports. Clinical ballistocardiograms have usually been recorded directly from the body of a subject on a solid table, or from a heavy platform with springy suspension. The purpose of this paper is to explain how both types of support distort the record and lead to erroneous interpretation of the cardiovascular nature of the waves. The point is important, because these distorted records are the basis both of the official nomenclature[3] and much of the clinical analysis to date.

## Part I. Artefacts in Dynamically Simple Ballistocardiographic Arrangements, with Light Platforms or None

We may make more vivid the artefacts in the simpler ballistocardiographic methods by noting the actual forces involved in the various arrangements used for recording. With a completely *free* suspension the principle of *static balance* would relate the small head-foot displacement ($y_b$)[3] of the heavy body ($m_b$), to the larger displacement ($y_c$) of the smaller cardiovascular masses ($m_c$): heart and blood. Equating the *moments*[A1] of these shifts of mass:

(a) $m_b y_b = m_c y_c$

$$y_b = \frac{.5 \text{ lb}}{150 \text{ lb}} \times .5 \text{ inches}$$

$$= .002 \text{ in. max. displacement of body as recorded by the BCG.}$$

($y_b$ and $y_c$ are measured from the common center of gravity: which is fixed, in the absence of external forces)

That is, the body displacement, $y_b$, is directly proportional to the displacement $y_c$ of cardiovascular masses under these conditions of negligible external force. It is important to note that these masses, $m_c$, are rapidly changing by at least a factor of 10 during the cycle.

To this static effect[4, 9] we must add the inertial forces[1, 2] which become important when cardiovascular masses are displaced with appreciable *acceleration*. The blood ($m_c$) entering the aorta may reach a velocity of 60 inches per second within 0.05 second, an acceleration, $\ddot{y}_c$, of 1200 inches per second$^2$ or 3.1 $g$[A1]. From the principle of *equal and opposite reactions* (inertial reaction of body = force from cardiovascular generator):

(b) $m_b \ddot{y}_b = m_c \ddot{y}_c$

$$\ddot{y}_b = \frac{0.1}{150} \times 1200$$

$$= 0.8 \text{ in/sec.}^2 = .002\, g = \text{max. acceleration of } m_b$$

where

$\ddot{y}_b$[A1] = acceleration of whole body mass $m_b$
$\ddot{y}_c$ = accel. of cardiovascular masses $m_c$

which produces an *inertial force* on the body of:

$$F_b = F_c = m_b \ddot{y}_b / g = 150 \times .8/384$$

$$= .3 \text{ lb} = 140 \text{ Gm.}$$

Again, with $m_b$ constant, $\ddot{y}_b$ measures not the acceleration of blood $\ddot{y}_c$, but rather the *force*

$m_c\ddot{y}_c$, in which $m_c$ is changing rapidly by a large factor[10]. The body motions (displacement and acceleration) so calculated account for the recorded head-foot ballistocardiogram: at least within the accuracy of the assumed motions of heart and blood and the validity of assuming the body mass to move rigidly as a whole, driven directly without yield by the cardiovascular forces. The free suspension mentioned is approximated by support on air springs, a very light, slow pendular platform[4, 9, 11, 12] or a bed in mercury or water.[12]

If the body does not move freely, the case becomes more complicated. All the ballistocardiographic supports now in use (except the mercury) involve some extraneous spring force which returns the body to a mid-position. The light pendular supports are brought into comparison with the older methods, by calculating an equivalent "spring stiffness," $k$, from their period ($1/f$) and mass. That is, for a spring oscillator:

(c) $2\pi f = \sqrt{k/m}$

or $k = 4\pi^2 f^2 w/g$

where $k$ = stiffness

$m = w/g$ = mass in inertial units ($g$ = 384 in/sec$^2$)

$f$ = natural frequency, excited by a tap on the head

This restoring stiffness multiplied by the ballistocardiographic displacement of 0.002 inches, gives the *spring forces*, $F$, shown in the last column of table 1. (In the direct-body method, the mass includes a 30 pound platform.)

TABLE 1

| Arrangement | Observed | | Computed | |
|---|---|---|---|---|
| | Frequency $f$(c/s) | Mass $mg$. (lb.) | Stiffness $k$(lb./in.) | Spring force $F$ (lb.) |
| Rappaport ..... | 0.25 | 160 | 1.0 | 0.002 |
| Burger ..... | 0.3 | 160 | 1.4 | 0.003 |
| v. Wittern..... | 0.5 | 160 | 4. | 0.008 |
| Nickerson..... | 1.5 | 180 | 40 | 0.080 |
| Dock, Smith.... | 4. | 150 | 240 | 0.480 |

Comparing the last column with the maximum cardiovascular force of 0.3 pound derived above, it is clear that in the last two cases the stiffness of the springy support must affect the motion. In general, this extraneous force is out of phase with the cardiovascular force. Furthermore, being periodic, it *confuses the aperiodic sequence* of systolic and diastolic impact detail.

Besides springs, a second extraneous force or artefact is present in current ballistocardiography. This is the force of viscous friction within tissues or structures in contact with the support: a force proportional to body velocity. In the free suspension method the peak velocity may be found by equating the *momenta*[A1] of body and blood at the instant of maximum ejection:

(d) $m_b\dot{y}_b = m_c\dot{y}_c$

$$\dot{y}_b = \frac{m_c\dot{y}_c}{m_b} = \frac{0.1}{150} \times 60 = .04 \text{ in/sec.}$$

$$= .1 \text{ cm./sec.} = 1 \text{ mm./sec., max BCG velocity of body.}$$

where $\dot{y}_b$ = velocity of body, assumed to move as a whole

$\dot{y}_c$ = peak velocity of blood

This extraordinarily small velocity generates, however, an appreciable *frictional* artefact in practical ballistocardiography. The low frequency arrangements of Burger, v. Wittern and Nickerson, whose "spring" artefacts are acceptably small, must still employ external viscous damping to reduce resonance at frequency of respiration. We can readily determine the *force* artefacts which result. If we limit peaking of the response at resonance to a 25 per cent increase ($Q = 1.25$: *resonance factor*) damping $r$ must be introduced to 0.4 of "critical damping" $r_c$.[5] This is usually measured in terms of the inverse quantity *zeta*:

$$\zeta = \frac{r}{r_c} = \frac{1}{2Q} = 0.4 \text{ the } \textit{damping factor} \text{ or } \textit{ratio}.$$

The existent damping force *per unit velocity*, $r$, (damping coefficient) is:

(e) $r = \zeta \cdot 4\pi fw/g$ Since $r_c = 2\sqrt{km}$
$= 4\pi fw/g$[14]

which gives, if we set $\zeta$ = 0.4, 0.4, 0.4 and 0.25, respectively, for methods of Burger, v. Wittern, Nickerson and Dock:

$$r = 0.6, 0.9, 6.0 \text{ and } 6.0 \frac{\text{lb}}{\text{in/sec}}, \text{ respectively.}$$

Finally, to get the actual damping forces, multiply these by the maximum body velocity (0.04 in/sec):

$$F \text{ (viscous)} = .025, .035, .24 \text{ and } .24 \text{ lb (max.).}$$

That is, the viscous force of the dorsal tissues in the Dock method is as strong as the heavy oil damper used with the Nickerson bed. It is clearly an artefact comparable with the force of cardiovascular origin (0.3 pound) we are trying to measure.

Since the frictional artefact opposes the *velocity* rather than the displacement or acceleration, it affects mainly the timing or delay of a transient response wave.[22] That is, the damping involved in low frequency beds and direct-body supports causes the recorded body movements to lag behind the cardiovascular forces which produce them by 50 to 120 msec. However, this is not a simple shift of the waves, but an irregular displacement varying with wave form. It affects both displacement and acceleration ballistocardiographic records in the important frequency region near body resonance.

Taken together, all these extraneous forces from constraints on the body, combine with the cardiovascular drive, $F_c$ as follows:

inertial reaction + damping force

+ spring resistance = cardiovascular force

or $m_b\ddot{y}_b + r\dot{y}_b + ky_b = F_c$ equation (1)*

We wish now to find the motion, $y_b$, of the body, compared with motion, $y_c$, of the cardiovascular mass, $m_c$. As this depends on frequency, it is simpler to solve by rewriting equation (1) in another standard notation:

(1a) $\ddot{y}_b + 2\zeta\omega_b\dot{y}_b + \omega_b^2 y_b = \dfrac{F_c}{m_b} = \dfrac{m_c\ddot{y}_c}{m_b}$

where $f_b$ = natural frequency of body
$\omega_b$ (omega) = $2\pi f_b$ called "angular" natural frequency,
$\omega_b^2 = k_b/m_b$ resonance factor, as in formula (c) above
$2\zeta\omega_b = r_b/m_b$ dissipation factor, as in formula (e) above

This is readily solved[A2] for any frequency, $\omega$,

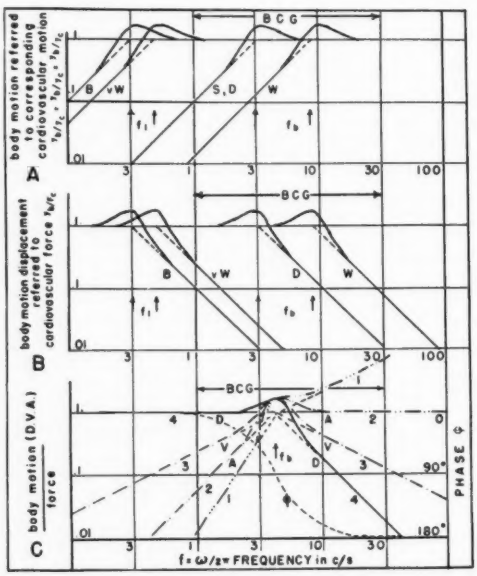


FIG. 1. Response spectra of "simple" ballistocardiograph systems. *A*. Asymptotic behavior of ballistocardiograph supports of Burger, v. Wittern, Smith, Walker, when referred to *corresponding* motions of cardiovascular materials: amplitude vs. frequency of *D*isplacement, *V*elocity or *A*cceleration (force); showing attenuation (at 12 decibels per octave) below resonance, flat above.

*B*. Displacement response referred to *force*, for same systems (D = direct body). Here the *higher* frequencies are attenuated, at same rate. The B and v.W. *displacement* records show negligible force in ballistocardiograph band.

*C*. Curves 4, 3, 2 show direct-body *D*isplacement, *V*elocity and *A*cceleration referred to *force*. Also, how body response depends on what aspect of cardiovascular motion it *refers* to, viz.: 1 = $\dot{y}_b/y_c$; 2 = $\dot{y}_b/\dot{y}_c$; 3 = $\dot{y}_b/\ddot{y}_c$; 4 = $y_b/\ddot{y}_c$. All are *related* by the multiplier $(f/f_b)^n$. Phase-shift vs. frequency ($\phi$) has same curve for all combinations, but its zero shifts.

* This equation of Newton-D'Alembert and its solution, have already been used to analyze the ballistocardiogram.[2, 4, 5, 28]

of the driving force, $F_c$, to give the relation derived in various textbooks[13, 14, 15] and used by Burger[4]:

$$(1b)\quad \frac{\text{body displacement}}{\text{"blood" displacement}} = \frac{y_b}{y_c} = \frac{m_c/m_b}{\sqrt{(1-\omega_b^2/\omega^2)^2 + (2\zeta\omega_b/\omega)^2}}$$

This relative response of body to blood motion is shown graphically in figure 1*A*, curve *D*. It rises with slope of 2 (on a log-log scale) to a peak, at resonance (where $f = f_b$ or $\omega = \omega_b$) then becomes flat at higher frequencies (without limit according to this equation). The amplitude decreases with body weight, but $m_a/m_b$ is nearly constant.

## Discussion

A. This relation should specially interest ballistocardiographers because it shows that with the essentially one-mass arrangements of Burger, v. Wittern, Dock, the *body displacement*, $y_b$, is proportional to cardiovascular *displacement*, $m_c y_c$, rather than to *force* $m_c\ddot{y}_c$ in the wide ballistocardiographic range *above* resonance with the support (fig. 1*A*). Below resonance (0.3 cycles per second, 0.5 cycles per second, 4 cycles per second, respectively) the body motion decreases rapidly with the square of forcing frequency if we refer this motion to *displacement* of cardiovascular tissues.

(1) With resonance set below .5 cycles per second (fig. 1*A*, B & v.W) the normal ballistocardiographic displacement record exhibits a very simple form[4, 16]: a sawtooth wave at heart frequency (ca. 1 cycle per second) hence with strong *third* harmonic component. It shows very little detail in systole or diastole. Elsbach[16] has discussed the clinical information in it. (2) With resonance set at 3 to 5 cycles per second (direct body) (fig. 1*A*, S,D) the third harmonic is much enhanced, but the slower cardiovascular displacements become attenuated and are overlaid in the *body displacement* record by the force component, to be discussed next.

B. We may examine how the *body displacement* in the ballistocardiograph range relates to the cardiovascular driving *force*, simply by dividing $\omega^2$ into equation (1b). This rotates curves 1*A* into 1*B* (fig. 1) whose equation is:

$$(1c)\quad \frac{\text{body displacement}}{\text{force on body}} = \frac{y_b}{m_c\omega^2 y_c} = \frac{y_b}{m_c\ddot{y}_c} = \frac{1/m_b\omega_b^2}{\sqrt{(1-\omega^2/\omega_b^2)^2 + (2\zeta\omega/\omega_b)^2}}$$

Since $\frac{1}{m_b\omega_b^2} = \frac{1}{k}$, the amplitude decreases with stiffness, $k$, of the support (whether dorsal tissue or pendulum), as well as with increased body mass.

This expression when plotted (fig. 1*B*) now becomes flat (invariant with frequency) *below* resonance. Thus for the oscillating body (Dock, Walker) the *displacement* of deflecting tissue springs now measures the applied ("cardiovascular") *forces*. Other factors being equal, with the stiffer tissue-coupling and higher resonances used by Walker (W, fig. 1*B*) more ballistocardiographic detail emerges: the "sand-pack" ballistocardiograph therefore better resembles the wide-band Rappaport ballistocardiograph[41] than does the Dock ballistocardiograph. Furthermore, the major cardiovascular impact intervals are less confused by the irrelevant periodicity of the body. Nevertheless, for frequencies *above* the 10 cycles per second resonance, the body's inertia still forms a high-cut filter. Conversely, above resonance the ballistocardiograph *force* information in the *displacement* record is attenuated: completely with the mercury, Rappaport, Burger and v. Wittern supports, largely in the Dock record and partially in the Walker—inversely with frequency[2] (at the rate of 12 db/oct[A3]).

C. The *velocity* ballistocardiogram recorded by these methods has a frequency spectrum identical with displacement, when referred to the *corresponding aspect* of the cardiovascular drive (fig. 1*A*). This is demonstrated by differentiating the left side once or twice:

$$(1d)\quad \frac{\text{body velocity}}{\text{blood velocity}} = \frac{\dot{y}_b}{\dot{y}_c} = \frac{\text{body acceleration}}{\text{blood acceleration}} = \frac{\ddot{y}_b}{\ddot{y}_c} = \frac{m_c/m_b}{\sqrt{(1-\omega_b^2/\omega^2)^2 + (2\zeta\omega_b/\omega)^2}}$$

exactly as before: where $f_b = \omega_b/2\pi$ is the resonance frequency. This expression is important because it shows that *above resonance* the body *velocity* ballistocardiogram correctly renders the cardiovascular *momentum* ($m\dot{y}_c$) (fig. 1*A*) and the *acceleration* ballistocardiogram the *force* on the body from the blood ($m\ddot{y}_c$) (fig. 1*A*). Sensitivity is again inverse with mass of body.*

One may legitimately ask if the velocity ballistocardiogram is "better" than the acceleration. If clinical study of the wave form of the *velocity* ballistocardiogram should prove to correlate in the faster details with important pathological changes, we might conclude that changes of momentum,[18] rather than force, are better indices in such cases. There is no a priori basis for preferring one of the three derivatives, *D*, *V*, or *A*. While, naively, each is simply the slope of the preceding, physically they really contain quite different kinds of information, linked in a way which changes at each stage of mechanical transmission. Both force and velocity are essential to describe a dynamical system,[14] just as voltage and current are for an electric system. Only clinical experience will tell which can best be spared. Intrinsically the displacement record, $y_b$, is lowest in detail (potential information); the acceleration, $\ddot{y}_b$, highest: but this relation is true of all complex curves. In ballistocardiography the acceleration is technically hardest to record. In the case of electrocardiography, the voltage (dynamically analogous to acceleration) is the easiest; its second integral (analogous to displacement) would be most uninformative.

D. The *acceleration ballistocardiogram* of a "single mass" system has been shown above to be flat with (proportional to) *force* for frequencies *above* resonance ($\ddot{y}_b/\ddot{y}_c$ in fig. 1*A*). As this is a region of force information rejected by the usual displacement records (curve *D*, fig. 1*B*) and evidence[19, 20] shows that certain clinical abnormalities correlate better with details of the direct body acceleration ballistocardiogram than with displacement, it is important to know whether the wealth of force detail appearing in this upper band is reproducible and significant.* Reproducibility indeed is a serious problem. For high frequencies the acceleration ballistocardiogram takes on mechanical complications. Even common observation shows that here the body is not the unitary oscillator implied in identifying the acceleration or displacement records with force on body. Above 7 cycles per second[21, 34] the abdomen, thighs, head, and other parts of the body begin to show separate resonances. Such phase differences in acceleration between different portions of the body are quantitatively demonstrated by a head-foot shaker applied to either end. While no adequate study of this segmentation vs. frequency has been made, it certainly differs between subjects and in one subject with slight variations in the mode of supporting the ankles. These considerations seriously affect the reproducibility and interpretation of the high frequency *acceleration ballistocardiogram*[20] taken from the shins.

E. *Phase error* between driving force and motion of the body (considered as a unit), appears only in the vicinity of resonance. It changes over a 180 degree range within a rather narrow band, depending on the body-damping ($\phi$ in fig. 1*C*). This large phase shift exists in displacement, velocity and acceleration, showing at resonance, respectively, 90 degree lag, 0 degree and 90 degree lead (vs. the drive force). So in the Dock and Smith methods, at 4 cycles per second the record is out of phase by 0.250/4 = 0.06

* Technically it is possible[17] to refer the body's displacement, velocity and acceleration (*D*, *V*, *A*) response characteristics arbitrarily at will, to the cardiovascular force, momentum or displacement. For example $\frac{\text{body velocity}}{\text{blood displacement}} : \frac{\dot{y}_b}{y_c}$ (curve 1, fig. 1*C*) *increases* above resonance. While this is an interesting exercise in keeping straight what one is referring to, such cross-references convey little meaning, except in the familiar case of $y_b/F_c$ discussed above.

* Technically, certain workers[17] find that the artefacts above 20 cycles per second are hopeless, and cut off the acceleration ballistocardiogram here with a sharp filter. Furthermore the usual shin pick-up senses an increase of floor noise above 20 cycles per second, which must be excluded. This, however, results from inadequate isolation of the pickup and is unnecessary.

second; in the Walker method at 8 cycles per second the lag is 0.125/4 = 0.03 second. This would be unimportant if it entailed only a simple timing shift of the ballistocardiograph pattern referred to the electrocardiogram. But the phase shift is not simple, because (with the damping which exists) it is not linear with frequency. Consequently each wave and wavelet has a different shift: a steep part shifts more in proportion than a gradual part of a wave; hence the phase lag caused by the body alters the waveform, (see part III). This type of distortion proves most serious when the resonance is located among the most prominent force details, in the 4 to 8 cycle per second region of the spectrum (fig. 1*C*). Experimental studies[22] confirm that phase lag depends on the wave form of the driving force.

Summarizing paragraphs A through E, we have shown how the various aspects ($D$, $V$, $A$) of the ballistocardiographic response, as recorded by the simpler methods, may be expected to vary with the driving frequency because of forces from the support which are *irrelevant* to the cardiovascular drive. With the direct-body method such forces create a resonance in the midst of the ballistocardiograph spectrum. This applies to the methods of Dock, Smith, Walker (and equally to the Starr method, part II). From this resonance arise two kinds of distortion: amplitude and phase (considered more quantitatively in part II).

(1) The amplitude distortion is especially serious in the 3 to 5 cycle per second region, because here the irrelevant body resonance is inordinately excited (a) by the timing of successive impacts in systole and (b) by the third harmonic of the blood displacement wave. That is, certain components of the cardiovascular force pattern cause a "ringing" of the body at this frequency. As a result the amplitude of the ballistocardiogram at resonance (a frequency surprisingly alike between individuals) is recorded at least twice as large as are equal force components at other frequencies. This factor ($Q = 2$) at resonance is determined by the damping ($\zeta = 0.25$) previously described, by the simple relation $Q = \frac{1}{2\zeta}$; i.e., the greater the body damping, the less the ballistocardiographic *amplitude* distortion.

(2) The phase distortion is a timing shift of the major ballistocardiogram waves by considerable amounts, according to their shape and size. This effect robs of quantitative significance the various comparisons of the ballistocardiogram wave timing with events in systole. Conversely, by moving resonance of the body (on its supports) out of the ballistocardiographic spectrum, Rappaport's[23] comparison of cardiovascular events with the ballistocardiogram wave sequence gains considerable credence, insofar as the phase errors arise mainly from the "somatic" oscillator. The phase error in the intermediate 1.5 cycles per second support[2] is still very serious, because the greater the damping, the more extensive the phase distortion.

(3) Another objection to ballistocardiograph supports which permit the body a resonance in the midst of the response spectrum, lies in the mixed physical interpretation. We have shown why the usual *displacement* ballistocardiogram should be interpretated as force ($F_c = m_c\ddot{y}_c$) below resonance, as cardiovascular displacement (moment $m_c y_c$) above, and between as a mixture (plus momentum $m_c\dot{y}_c$). But since $m_c y_c$ contains little that is rapid,[4] the sharp attenuation of displacement response above 8 cycles per second dominates the record and yields the general impression[4, 24, 25] that little force of higher frequency exists. However, in the *acceleration* ballistocardiogram well *above* resonance the record comes to mean cardiovascular force, and its small, rapid features display much systematic force detail rejected by the displacement ballistocardiogram; but now, *below* resonance this record means $\frac{d^2}{dt^2}$ (force)—a quantity not defined physically—in a frequency band where the *forces* are physiologically minimal. And the "mixed" region near direct-body resonant frequency, where *neither acceleration nor displacement can be interpreted as driving force*, lie the major peaks of the records described by Dock, Smith, Arbeit and Starr.

To deal with this unsatisfactory situation

for studying ballistic forces, one can indeed record *both* displacement and acceleration.[17] This solution sacrifices the *relation* between fast and slow components, just as would a phonograph record played first with a "woofer" alone and then with a "tweeter". However, it is so practical to remove the root of the difficulty by recording acceleration from soft suspensions,[4, 12, 23] that it seems unwarranted to load case histories by multiple ($D$, $V$, $A$) records of the head-foot aspect alone. With these soft suspensions, the acceleration record may legitimately be interpreted as "force" for all frequencies until the body becomes seriously fractionated in oscillation.

Several investigators have attempted to modify this resonant state of the body in mid-spectrum, recognizing that the support radically affects the ballistic record. Walker and coworkers[8] have shown that softening pads under the body reduce the resonant frequency but little (for mechanical reasons discussed in part II); however, stiffening the body-coupling to ground does effectively move the resonance upward well away from the sensitive 3 to 6 cycles per second region. This can be done with constraints at shoulders and feet, sand-bagging, or by encasing the body or parts of it in putty or sand. The increased stiffness involves mainly the addition of further tissue springs in parallel but some nonlinearity probably enters as one begins to push on the bones through the skin. To double the body frequency to 8 cycles per second in this way requires quadrupling the stiffness: a painful limit when pressing on shoulders and feet alone.[12] When sand is used, the mechanics becomes more complex. Apparently the leg joints become more compliant when not compressed, for the legs in sand at higher frequencies seem to move but little. Hence the body becomes more complicated dynamically, and in a way which varies greatly between individuals.[26] So part of the increased resonant frequency (10 cycles per second) in sand should be attributed to reduced vibrating mass.

Certain features of this line of investigation are promising. With resonance so high, the more rapid detail in the displacement ballistocardiogram[17] instead of being rejected, is now extra strong (fig. 1*B*). The tracing recorded from thorax or head is less remote and may be less variably coupled than that from the shins. With sand-pack, the relative immobilization of legs reduces the number of vibrating elements being recorded at the higher frequencies. The reduction of vibrating mass should magnify the output, and so improve the "signal-noise" ratio.

Several objections are important. The resonance (about 10 cycles per second) is still in mid-spectrum, with at least half the ballistocardiographic range[27] distorted and attenuated, so that the really fine detail of the systolic pattern is not seen. In many cases the damping factor is low, so that resonance afflicts the pattern with spurious aftervibrations and falsely enhances any features happening to be at resonant frequency. The sensing location on the body is poorly defined dynamically, reducing reproducibility. Finally, patients exhibiting apprehension when packed, or the very sick, could hardly be regarded as in proper relaxation for ballistocardiograph testing.

Since no amount of constraint seems to raise the body's frequency high enough in the spectrum to escape distortion of the record from body resonance, the remaining alternative seems to be that of the ultrasoft supports. Successive developments[2, 4, 5, 9, 11, 12, 23, 24] of these, and the corresponding analyses,[2, 4, 5, 28] have overcome the early difficulties and show fair agreement of behavior with theory.[29]

## Summary, *Part I*

We have reviewed the mechanically simpler arrangements for ballistocardiography in which the platform effect is negligible or absent. It is shown how the method of supporting the body can introduce major artefacts into the record.

After calculating the forces on the body arising from its support or coupling to ground, and assuming the body to be a unit, we have described their effect quantitatively across the ballistocardiograph spectrum: whether of displacement, velocity or acceleration. The distorting effect of the body itself as a mechanical "filter" has been illustrated in this way, both in amplitude and phase.

We have emphasized the importance of stating to what aspect of cardiovascular dynamics the recorded ballistocardiogram is referred. The current methods of recording whose coupling to ground produces resonance within the ballistocardiograph spectrum, (Dock, Smith, Starr, Walker) may all be called "compound" records. That is, at low frequencies the *displacement ballistocardiogram* refers to driving force, near resonance to driving momentum, and above resonance to driving displacements (mass moments). This mixing of dynamic aspects does not occur when resonance of the system is set below the ballistocardiograph spectrum. Records from the latter systems may be called "simple" in the sense of showing the respective dynamical variables in displacement, velocity and acceleration in a consistent way across the ballistocardiograph spectrum. This would seem prerequisite to a study of forces, for example.

In part II we will examine the artefacts in those current arrangements which measure the motions of *platforms* (Nickerson, Starr). The platform weight creates a high-frequency error or artefact especially strong in such beds, but which turns out to affect appreciably the light pendular beds also. The measurement of such platform artefacts, their effect on ballistocardiograph records, and their elimination, are the main interest of this paper. The randomness and erroneous information introduced by these supports is especially important because the official nomenclature of the wave form is based on them, as well as most of the clinical analysis of the last 10 years.


## Summario in Interlingua

Le arrangiamentos dynamic de Dock, Smith, Walter, Nickerson, Burger, e. v. Wittern resimila systemas a massa unic in le area ballistocardiographic inter 1 e 10 cyclos per secunda. Nos demonstra que in methodos a registration directemente ab le corpore, le supporto adde forte non-desirate componentes al fortias cardiovascular e assi deforma seriemente le resultante registration, specialmente in le importante region inter 4 e 8 cyclos per secunda.

Le varie registrationes—illos de displaciamento, de velocitate, de acceleration—ha non solmente un, sed plure significationes dynamic, dependente de si illos se refere al displaciamento o al momento o al fortia cardiovascular. Per consequente un registration directemente ab le corpore (con resonantia con le banda de passante frequentias del ballistocardiographo) es ambigue: le registration total non pote esser referite a ulle unic aspecto del dynamica cardiovascular. Ergo un registration ab un supporto del typo a corpore directe non pote correctemente esser designate como un ballistocardiogramma de "fortia."


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*Appendix 1.*

*The Kinetic Quantities are*:

$y$ = (head-foot) displacement, $\dot{y} = \dfrac{dy}{dt}$ = velocity

$$a = \ddot{y} = \frac{d^2y}{dt^2} = \text{acceleration}$$

$x$, $y$, $z$ = respectively the R.L., H.F., and A.P. directions in ballistocardiography.

In a time trace, $\dot{y}$ measures the slope and $\ddot{y}$ the *curvature* at a wave tip.

Elsewhere, the curvature is $\kappa = 1/\rho = \ddot{y}(1 + \dot{})^{-\frac{3}{2}}$ where $\rho$ = radius of curvature.

*The dynamical quantities are*:

$my$ = *Moment* (of displacement): unbalancing effect of displacement of blood.

$F \times t = m\dot{y}$, *Momentum*, or potential impulse, measured by the velocity change of mass $m$.

$= I$, *Impulse*, measured by a force $F$ acting through time $t$.

$F = m\ddot{y}$, *Force*, measured by the acceleration, $a$, it imparts to an unimpeded mass $m$ or by the rate of change of momentum: $\dfrac{d}{dt}(mv)$

$T = \frac{1}{2}\, m\dot{y}^2$, *Kinetic energy*, (work, proportional to the square of velocity

$V = \frac{1}{2}\, ky^2$, *Potential energy*, (work stored in a spring of stiffness $k$ when compressed a distance $y$, exerting spring force $F_s = ky$ to stop $m$

The mass, $m_b$, of the body, is assumed concentrated at the body's center of gravity (near waist), but acted on *directly* by the moments, momenta and forces of the heart or slug of blood $m_c$, growing, contracting and moving in the thorax during the cardiac cycle.

The symbol $g = 32 \times 12 = 384$ in/sec$^2$ (inches per second per second) is the acceleration of any body falling freely toward the earth. This symbol $g$ occurs in many equations because the inertial mass of a 1 pound weight is $\frac{1}{32}$ "slugs" (the unit of mass in the English system).

*Appendix 2.*

The equation for motion of body is solved most rapidly by the method of rotating vectors at a single frequency $f = \omega/2\pi$:

(a) Substitute in equation (1a) page 580, the following vector expressions for force and motion and their derivatives, at frequency $\omega$:

$$y_c = \bar{y}_c e^{j\omega t} \qquad \dot{y}_c = j\omega y_c \qquad \ddot{y}_c = -\omega^2 y_c$$

$$y_b = \bar{y}_b e^{j(\omega t+\varphi)} \qquad y_b = j\omega y_b \qquad \ddot{y}_b = -\omega^2 y_b$$

where $\bar{y}$ = amplitude

$\varphi$ = phase lag at frequency $\omega$

$\epsilon^{\exp}$ gives angle of vector at time $t$.

Eqn. (1) becomes $(\omega_b^2 - \omega^2 + 2j\zeta\omega_b\omega)\bar{y}_b e^{j(\omega t+\varphi)}$

$$= \frac{m_c}{m_b}\,\omega^2 \bar{y}_c e^{j\omega t}$$

To get the amplitude, simply multiply each side by its conjugate, giving:

$$[(\omega_b^2 - \omega^2)^2 + (2\zeta\omega_b\omega)^2]\bar{y}_b^2 = \frac{(m_c\omega^2)^2}{m_b^2}\bar{y}_c^2$$

This yields the ratio of output motion, $\bar{y}_b$, to input motion, $\bar{y}_c$, shown in the text, equation (1b)

*Appendix 3.*

The notation decibels per octave (*db/oct*) is in general use to describe the attenuation of "signal" by transmission thru a physical system. A factor of 2 = 6 db (6 = 20 log 2), 12 db = factor of 4, 20 db = factor of 10. The *octave* or doubling of frequency is the unit of frequency change most common in communications parlance; our graphs are cycled in *decades* of frequency.

*Appendix 4.*

An inertial force was taken from a light eccentric shaker, and made constant by changing its moment (mass × distance) with the square of frequency of rotation. A later model of shaker applied a constant force also, externally to the driven mass, regardless of its frequency, motion or resistance. To do this, a sinusoidal displacement (large compared with the output) was applied to a spring at the end opposite to the mass being driven.

*Appendix 5.*

The parameters $m_b$ $k_b$ and $r_b$ for a person were obtained by recording photoelectrically the displacement of the shins after a small displacement of head or feet. If we assume $m_b = \omega_b/g$ to be the whole mass of the body, from the damped oscillation which follows a tap on the head, the *stiffness*, $k_b$, of the body referred to its support is best found from the measured *frequency*, $f$, using the basic relation $f = \frac{1}{2\pi}\sqrt{\frac{k_b}{m_b}}$.

Stiffness, $K$, is also obtainable from Hooke's law: $K = F/d$, where $F$ is a static force applied and $d$ is the resulting deflection. This results in a *different* body stiffness, because it introduces additional springs where the test-force is applied.

The ratio $d/F = \frac{1}{K}$ = "compliance" or yield per unit force has been used to describe the sensitivity of ballistocardiograph beds.[1, 2] This procedure is valid when the platform is moved only by static forces, i.e., no dynamic (inertial) forces are involved. This is not true for most ballistocardiograph beds.

The *damping* of a body or bed may be obtained experimentally in three ways. (a) On the record of the decay of damped oscillation after a displacement, if $y_2$ and $y_1$ are two successive peaks, then the "logarithmic decrement" is $\lambda = \log_e \frac{y_1}{y_2}$ which is easily plotted on logarithmic paper. This yields the damping *ratio* $\zeta = r/r_c = \lambda/2\pi$, *provided* $\zeta > 0.5$, from which we get the damping *coefficient* used in the differential equation (1a) $r = \zeta r_c$

where $r_c$ = critical damping coefficient

$$= 4\pi fm = 2\sqrt{km}$$

critical damping $\zeta = 1$ being the value where, upon release, overshoot just fails to occur. For heavy damping ($\zeta > 0.5$) the method of Warburg[52] may be used.

(b) The number, $N$, of oscillation *periods* required for amplitude to decline to 37 per cent, also gives the damping ratio: $\zeta = \frac{1}{2\pi N}$. The supine body damps rapidly: $N = 0.67$ period approximately, giving $\zeta = 0.25$. With such rapid damping both $N$ and $\lambda$ are difficult to measure accurately in practice.

(c) If a constant force shaker[A2] can be used, $\zeta$ may be obtained from the relative amplitude or $Q$ of a resonance peak. By definition

$$Q = \frac{2\pi fm}{r} = \frac{r_c}{2r} = \frac{1}{2\zeta};$$

when $\zeta = 1$ $Q = .5$

$\zeta = .5$ $Q = 1$

$\zeta = .2$ $Q = 2.5$

The body damping being about 0.25, $Q = 2$.

*Appendix 6.*

The mechanical model shown (fig. 2*B*) has a simple and exact electrical analog, figure 2*C*, explored independently by v. Wittern,[5] unknown to us, somewhat prior to our work. Its parameters adjust more easily than those of a mechanical model and it calculates virtually instaneously. The results are identical with a mathematical solution but variants can be explored more readily; in particular the approach to optimal ballistocardiograph design.

Before turning to this simpler analog method, we determined similar frequency "characteristics" by solving equations (2) on a Reeves integrating-computer (differential analyzer). The integrating-computer produces $\dot{y}$ and $y$, as integrals of $\ddot{y}$, introduces the body and platform coefficients, and makes the additions indicated in the force equations. For any sinusoidal force component $F_b$ of frequency $f$, the computer records the ballistocardiograph platform motion $y_p$ in phase and amplitude. From this one can plot the response characteristic vs. frequency.

Conversely, given a *known* ballistocardiograph curve $y_p$, the computer delivers the force pattern $F_b(t)$ required to drive the body-bed system in just this way (part III). There is no experimental way to get this directly because one cannot apply forces to the skeleton just as the heart and vessels do.

# The Effect of Nitroglycerine on the Ballistocardiogram of Persons with and without Clinical Evidence of Coronary Heart Disease

*By* Isaac Starr, M.D., Elaine Pedersen, M.D. and Aldo N. Corbascio, M.D.

Nitroglycerine has been given to a series of patients and its effect on the ballistocardiogram observed. Attacks of angina pectoris are accompanied by great deterioration of the record; if nitroglycerine is given at such a time, the record improves as pain passes off. Given between attacks to patients having coronary heart disease with abnormal ballistocardiograms, nitroglycerine is often followed by improvement in the record. Also given to older patients who have abnormal ballistocardiograms but no clinical evidence of coronary heart disease, nitroglycerine is often followed by improvement in the record, a fact consistent with the view that coronary heart disease is present in such cases. However, nitroglycerine is sometimes followed by deterioration of the ballistocardiogram, the possible reasons for this unexpected finding are discussed; attention is called to recent evidence indicating that serious toxic effects may follow exposure to nitrites in industry.

CLINICIANS of the physiologic school will not long be satisfied with the description of abnormalities of cardiac performance occurring under conditions of rest, although this is obviously the way to begin such studies. One can expect to gain important information by comparing the reactions of normal and diseased hearts to standard tests of many types. Thus, the response to nitrites has been used by clinicians for many years as an aid to diagnosis. The regular relief of pain in the chest after amyl nitrite or nitroglycerine is accepted by many doctors as evidence that the patient is suffering from angina pectoris and coronary heart disease; for, although it is well known that nitrites may at times relieve pains originating elsewhere than in the heart, this seldom occurs with the rapidity or with the regularity which characterizes the relief of angina pectoris by these drugs.

It is of great interest to study the association between physiologic and anatomic abnormalities even though one has no expectation that the one will be found pathognomonic of the other. So it seemed that the administration of nitroglycerine to patients on the ballistocardiograph would provide a test of importance. Such a test would enable us first to observe the effect of this agent on the cardiac performance of patients diagnosed as suffering from coronary heart disease by the usual clinical criteria, and then to discover whether this response was shared by other patients in whom the presence of coronary heart disease was unlikely or uncertain.

On the basis of such findings, we hoped to be in a position to throw light on a very interesting problem. Everyone taking ballistocardiograms in large numbers has found many persons past 50 years of age[1, 3, 4] whose records were abnormal in form, although their history and clinical findings gave no clear indications of cardiac abnormality. Similar abnormalities of ballistic form have been found rarely, if at all, in healthy young adults, but they have been found frequently in persons suffering from angina pectoris and in those who have had cardiac infarction.[1, 2] Both this similarity, and the fact that the increasing percentage of ballistic abnormalities, found in the living as age advances, corresponds quite well with the increasing percentage of coronary heart disease found at necropsy as age advances,[6] raise the

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question whether the finding of an abnormal ballistocardiogram in an apparently healthy person does not indicate coronary heart disease at an earlier stage than that which can be identified by the appearance of the usual clinical syndromes.[7] While the reported data are still meager, this view finds support in the necropsy findings of persons who have had abnormal ballistocardiograms during life[2] and in the still few but increasing reports of persons having abnormal ballistocardiograms when apparently in good health, who have later developed clinical coronary heart disease.[3, 4] We will take this opportunity to report another such case, followed 16 years to necropsy.

Accordingly, the response to nitroglycerine has been used as a standard test in over 100 patients, and in a smaller number of healthy persons. We have found numerous instances in which ballistocardiograms, abnormal in form, have been improved, or even restored to normal during the action of nitroglycerine. Such improvement was found most frequently in patients readily diagnosed by the ordinary clinical criteria as having a coronary heart disease. But similar improvement after nitroglycerine was also found in the records of some patients in whom this diagnosis could not properly be made by such criteria. And to our surprise, deterioration of the ballistocardiogram after nitroglycerine was encountered frequently.

## Apparatus

A new high frequency ballistocardiograph, made for this laboratory by the Technitrol Company, employed with a Sanborn Twin-Viso recorder, proved ideal for the purpose of this study as the records could be read during the experiment as soon as they were written. The steel supporting frame of this new instrument is extremely heavily built, weighing 270 pounds. The table frame is of 635T5 aluminum alloy, the stiffening rods are of Dural. The table surface is of plywood, the total table weight being 42 pounds. The table suspension is 5 cm. in length. The pick up unit is an RCA 5734 electromechano transducer tube. The vibration properties of the table are; when unloaded, 26 cycles per second; when loaded with 100 pounds of iron bars, 14 cycles per second; with 160 pounds, 11.8 cycles per second; with 200 pounds, 10.4 cycles per second; rates slightly faster than those of our previous instruments, although the broader table of the new instrument is 15 pounds heavier than that of one of our older ballistocardiographs.[8]

When loaded with iron bars and deflected by a force of 500 Gm., a force equivalent to those recorded in large ballistocardiograms, sudden release is followed by a return to the base line in less than 0.04 second which is not instantaneous, but rapid enough to record ballistocardiograms. There is practically no overshooting after such release. No damping has been added and that inherent in the system is insufficient to damp out the fine vibrations imparted by the perpetual motion of the building when there is no subject on the table.

The records secured by this new instrument are almost exactly similar to those obtained by our older instruments,[5, 9, 10] but we have the impression that there are a few minor differences. The new records often show more definition in the early diastolic complexes, the L wave is less prominent and the M-N segment tends to be sharp and straight, so that this part of the newer records looks less like a series of waves in phase than in many of our older records. Also, we have the impression that we see short or absent K waves more frequently than in records secured by our oldest instrument, and in some healthy persons a doubled J peak is seen. So the form of the records is not very different from those secured by Talbot and his associates,[11] and by Deuchar and co-workers[30] by recording acceleration from a subject lying on a table floating in a pool of mercury, and those obtained by von Wittern,[12] by Burger[13] and by Elsbach[14] recording acceleration from a subject lying on a low frequency table, although our records are probably not identical with any of these. Theoretically[12] if all these instruments were perfect and if the properties of the body produced no distortion, or similar distortion, all these records should be identical, and they would record the forces; we find it gratifying that the differences are so small. Whether the gain in accuracy, expected because of the theoretical advantages of the newer technics, will compensate for the increased complexity and cost of apparatus, and the greater difficulty of maintenance and of calibration, cannot be foretold at this moment, as the use of these new methods in routine clinical work is just beginning.

## Results

The experience with the effects of nitrites on the ballistocardiogram can best be divided into two parts.

### *The Effects of Nitrites on the Ballistocardiograms of Healthy Young Adults*

For many years the senior author conducted a part of the undergraduate course in pharmacology in which familiar drugs were given to the students themselves. After receiving the drug, the subject reported his sensations while

his mates gathered around and made observations which included pulse rate and blood pressure. After our first ballistocardiograph had been constructed, these demonstrations were conducted with the subject lying on this instrument, and records were taken at intervals before, during and after drugs' actions. From these class experiments, we have records of the action of nitroglycerine in 15 healthy young adults, and of that of amyl nitrite in 13. These records were re-examined as part of this study. Recently we tested three additional healthy young adults with nitroglycerine.

*Results.* The results of this experience can be summarized in a few words. All the healthy young adults gave normal ballistocardiograms before the drug was administered. After inhaling amyl nitrite, as the face flushed and blood pressure fell, the heart rate accelerated and the ballistocardiogram increased in amplitude, its form remaining normal except in two cases when a very rapid heart rate was accompanied by such fusing of waves that the I wave was diminished. One or two tablets of nitroglycerine (each 0.6 mg.), placed under the tongue, had very little effect on these healthy persons lying at rest; blood pressure diminished little, if at all, pulse rate usually increased slightly and the ballistocardiogram either showed no noteworthy change or increased slightly in amplitude, its form always remaining normal.

### *The Effect of Nitroglycerine on Patients and Older Persons*

The patients employed in this study were secured from the medical wards or outpatient departments of the University Hospital. They do not represent a cross section of this population for we sought especially cases with abnormal ballistocardiograms, and we gave nitroglycerine to 83 such patients, most being over 50 years of age. We also gave nitroglycerine to 33 patients almost all in the latter half of life, who had normal records.

*Technic.* All the subjects came to the laboratory two hours or longer after their last meal. They lay supine on the ballistocardiograph for a 15-minute rest period, and then the control record was taken. This record was inspected and the decision whether to give nitroglycerine made. One tablet of nitroglycerine, 0.6 mg., was then placed under the tongue and records were taken at 2, 5, 7, 10, 15 and sometimes 20 minutes thereafter, blood pressure being determined just after each record by the auscultatory method, the points both of muffing and disappearance of sounds being recorded.

*Results.* Nitroglycerine caused a moderate fall in blood pressure averaging 14.9 mm. Hg for the systolic and 4.7 mm. Hg for the diastolic pressure. Our data on this response is skewed by the fact that the drug produces a greater fall of blood pressure in patients with hypertension than in those with normal pressure, as has long been known.

Some acceleration of the pulse rate was usually seen after the drug, but this change was small and transient, in the last 31 cases the maximum increase averaged 12.5 per minute. The figures give typical examples of the pulse rate and blood pressure changes. Flushing of the face was seen occasionally, and a few patients noted slight headache after the drug. Thus the typical and familiar effects of the drug regularly manifested themselves during our experiments.

Inspection showed that the maximum effect of the nitroglycerine was usually manifested in the record taken seven minutes after the administration of the drug; in that taken 15 minutes after the drug had been given this effect had largely or completely passed off. Thus the effect of the drug on the ballistocardiogram was transient.

In this study we have concerned ourselves only with large changes, so we relied on inspection of the records, and did not resort to measurement; only qualitative differences have been recorded. Improvement in the form of the record could be detected only if the original ballistocardiogram was abnormal in form; but deterioration of the record, or no change, could be detected irrespective of the character of the original record.

Examples of typical records showing the various changes which followed the drug are given in the figures. Figures 1 and 2 show ballistocardiograms and electrocardiograms secured before and during attacks of angina pectoris which appeared spontaneously, as well as records secured after nitroglycerine had

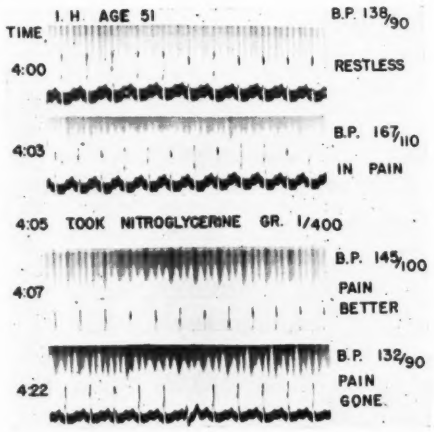


FIG. 1. Disorganization of the ballistocardiogram during an attack of angina pectoris and its restoration by nitroglycerine. Subject Dr. I. H., age 51, male. This patient had been previously tested on Oct. 2, 1951 and at that time he complained of pain in the left shoulder and the diagnosis was uncertain. In his note written at that time, Dr. Calvin Kay, the cardiac consultant, wrote, "The pain described could be of coronary origin although, if so, it is certainly atypical. It suggests more a referred pain from some structure in the region of the diaphragm, or from the spine." Indeed, an orthopedic consultant diagnosed arthritis of the cervical spine. The ballistocardiogram in 1951 was abnormal; in the smaller complexes of the respiratory cycle H far exceeded J in height and J was notched or flattened. Later he began having pain more typical of angina pectoris; although located chiefly between the shoulder blades, it was squeezing in character, brought on by exertion and relieved by nitroglycerine.

On May 24, 1954, before coming to our laboratory, he had been seen again by Dr. Kay who found a blood pressure of 132/90–88 mm. Hg. He lay quietly on our original ballistocardiograph for 15 minutes but it was noted that he seemed uncomfortable by the time the first record was taken. This is the first record reproduced above. Soon thereafter he said, "I now have the kind of pain for which I take nitroglycerine". The second tracing reproduced above was taken immediately and his blood pressure was found to be 167/110. Although lead II of the electrocardiogram was essentially unchanged during this attack one notes the marked deterioration of form in the smaller complexes of the ballistocardiogram, H far exceeding J in height and the latter wave being notched or flattened. The subject then took his usual dose of nitroglycerine (gr. 1/400). The record taken two minutes later is the third record reproduced above and it shows improvement in form and amplitude; at this time the pain was better and the blood pressure had fallen to 145/100. Pain disappeared about two minutes later and additional records, taken every few minutes thereafter, were quite similar to the fourth record reproduced above. They show that further improvement in the ballistocardiogram took place after pain had passed off. In the fourth record reproduced above the larger complexes are beginning to look normal, but H still exceeds J in height in the smaller complexes, so the record cannot be passed as normal.

One also notes that this is another case in which an abnormal ballistocardiogram was found before the development of the typical clinical picture of coronary heart disease.

These records were taken by the older technic; the reproductions are about one-third actual size.

relieved the pain. Figure 3 shows the results secured in a case of angina pectoris given nitroglycerine between attacks. Figure 4 shows the maximum improvement of the records of four patients. Figure 5 is an example of a deleterious effect, figure 6 of a mixed effect.

As will be seen from the figures, no particular feature of the ballistocardiogram is affected by nitroglycerine to the exclusion of others. Many sorts of abnormalities may disappear after nitroglycerine. We are particularly impressed by the changes early in systole which may follow the drug. The abnormally large H waves so often seen in cases of coronary heart disease, frequently disappear after nitroglycerine, a fact of interest because of the uncertainty of the physiological origin of the abnormal H waves in such cases. Other changes seen frequently after nitroglycerine are the deepening of shallow I waves, and the disappearance of notches on the J wave or the H-I or I-J segments. Increased amplitude of the record is common after the drug. The figures show the variety of changes which may follow the drug better than they could be described.

### *Relation of the Response to Nitroglycerine and the Clinical Diagnosis*

For the purposes of this study the 132 cases were subdivided into the five groups given in table 1. In the first group have been placed 48 patients who suffered from such typical attacks of angina pectoris that the diagnosis was not in doubt. They described attacks of pain, or of a sense of constriction, usually substernal, but sometimes located in other parts of the chest, brought on chiefly by exercise and relieved by rest and by nitroglycerine. Some of these cases

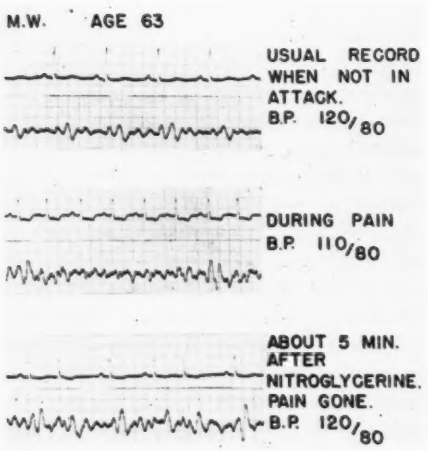


Fig. 2. Disorganization of the ballistocardiogram during an attack of angina pectoris and its restoration by nitroglycerine. Subject M. W., aged 63, male. This patient had suffered from severe angina pectoris for several years and ballistocardiograms had been secured at intervals during this time. He had received $I^{131}$ in May 1953. The top record is a good representation of those usually secured, and it is rather more normal in appearance than that of most cases having such severe angina. But the record cannot be passed as normal. The amplitude is too small—49 per cent below the normal young adult mean—and the smaller complexes are abnormal in form, the I wave not penetrating the base line in many. His blood pressure was usually 120/80 mm. Hg.

On June 29, 1953 he walked into the laboratory complaining of pain. He was placed on the table and after about five minutes of rest while the amplifiers were warming, the second record reproduced above was secured. He was in pain at this time, there was S-T depression in the electrocardiogram, amplitude of the ballistocardiogram was reduced and the form completely disorganized. At this time, blood pressure was 120/80 mm. Hg. He was then given 0.6 mg. nitroglycerine and pain was relieved in a few minutes. The third record reproduced above was taken five minutes later. Marked improvement in both electrocardiogram and ballistocardiogram is obvious, although the latter record is not altogether normal. At this time the blood pressure was 110/80 mm. Hg.

This patient is being followed closely and records at subsequent times when he was not in pain have resembled the first reproduced above. In these and in records shown in the following figures, the reproductions are about one-third the actual size. They were taken by the newer technic, using a Sanborn, Twin-Viso recorder.

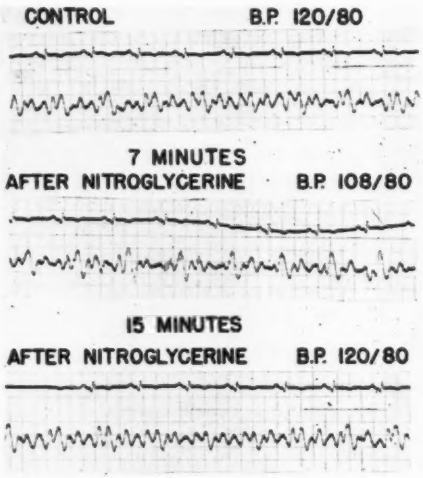


Fig. 3. Simultaneous ballistocardiograms and electrocardiograms taken before, during and after the action of nitroglycerine.

Subject G. B., age 42, male, weight 173 pounds. The patient had suffered a posterior wall myocardial infarction three months before this test. There had been some chest and shoulder pain since, but no typical angina. X-ray films showed the heart to be somewhat enlarged. Electrocardiogram was interpreted as indicating a well healed posterior infarct. Note the most abnormal control ballistocardiogram. The H wave is huge and its time relations with the electrocardiogram are abnormal. The I wave only rarely penetrates the base line and often fails to reach it. The ballistocardiogram taken seven minutes after nitroglycerine shows great improvement in the record, which is now about normal. The abnormal H wave has disappeared and the J peak has moved forward, in relation to the R peak of the electrocardiogram. The I wave is normal in most complexes, although it is too shallow to be passed as normal in some. The third record shows that the effect of the nitroglycerine had passed off within 15 minutes, so the improvement was temporary.

gave a clear history of a previous cardiac infarction and some did not. Their ages ranged from 88 to 29 years, the latter a case of congenital hypercholesterolemia.

In the second group 15 cases were placed who had a clear history of previous cardiac infarction with typical electrocardiograms, but who did not suffer from angina pectoris after recovery from the acute attack.

In a third group we placed several cases who, although lacking a clear story of either angina pectoris or coronary occlusion, were

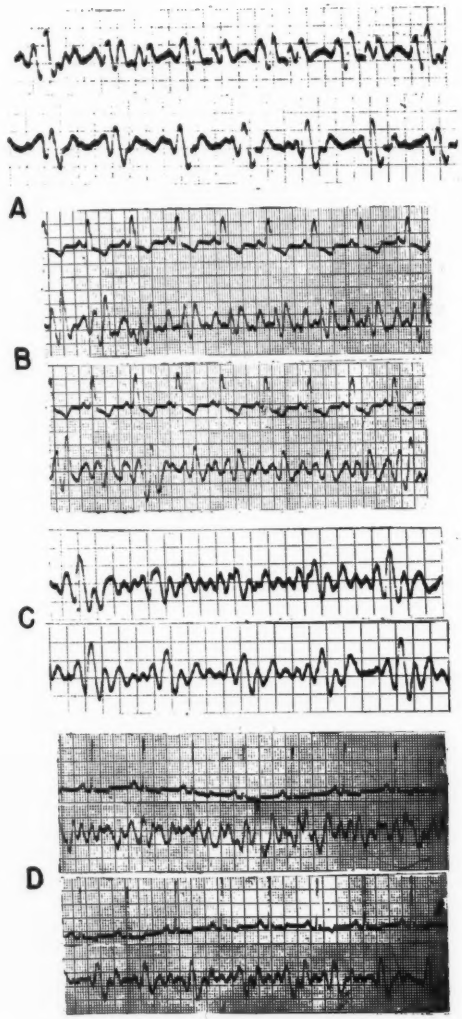


Fig. 4. Ballistocardiograms before and during the action of nitroglycerine. A. Records of: P. B., aged 50, a male who had had hypertension for many years and typical angina pectoris for six years, severe recently. High thoraco-lumbar sympathectomy one year ago with the aim of ameliorating the angina. In control period blood pressure was 180/110. Note high H waves in first record; they equal J in height in the smaller complexes of the respiratory cycle. The second record was taken seven minutes after nitroglycerine, the blood pressure being 140/90. Note that this record as a whole is much more normal in appearance. Note the disappearance of the abnormal H waves; K is deeper than in the control but this is not abnormal for a man of his age.

diagnosed arteriosclerotic heart disease by the clinician in charge because they were elderly persons with many signs of cardiac abnormality, and no other etiology was apparent.

B. Simultaneous electro- and ballistocardiograms of: B. S., aged 43, male. Cardiac infarction had been diagnosed from an episode in the past on doubtful grounds. The patient had atypical chest pain more recently. These pains were accompanied by shortness of breath, often brought on by exercise. They were not promptly relieved by rest. There was questionable cardiac enlargement by x-ray study. Bundle branch block was present constantly and gallop rhythm had been heard at times. The upper record is the control, the blood pressure being 126/90. The H waves are greatly enlarged, sometimes equalling J in height. K is short in many complexes and the diastolic ballistic components are clearly evident. The second record was taken seven minutes after nitroglycerine. Note that the H wave has diminished to normal size and the record would be passed as normal.

C. Ballistocardiograms of M. K., age 57, male. The patient complained only of atypical pain in his left shoulder, not usually related to exercise. It tended to be present in the morning. It had been relieved temporarily by heat and manipulations of the shoulder. The first record is the control, the blood pressure being 140/80. The form is not normal, for the J peak of the smaller complexes is notched or flattened. The second record was taken seven minutes after nitroglycerine, blood pressure being 120/80. Note that ballistic abnormality has disappeared.

D. Simultaneous electro- and ballistocardiograms of P. S., aged 58, male. The case was a confused one. The chief complaints were cough, shortness of breath and sharp stabbing pain in right chest with radiation to right upper abdominal quadrant and right shoulder. X-ray films showed rounded mass in right chest with interlobar fluid collection. The tubercle bacillus was not demonstrated in the sputum. Bronchoscopy revealed little. The urine was constantly abnormal and pyelonephritis was diagnosed. Blood urea nitrogen varied from 20 to 46 mg. per 100 ml. There was slight anemia and both a duodenal ulcer and a polyp of the colon were demonstrated by x-ray examination. Electrocardiogram suggested left ventricular strain. The heart was slightly enlarged. There was no history suggestive of angina pectoris and the pain was believed to be due to the pulmonary lesion. This was never diagnosed and he was considered too sick for exploration.

The first record is the control, taken when the blood pressure was 134/94. Note the extreme abnormality of ballistic form; without the simultaneous electrocardiogram, systole could not be located. The second record was taken seven minutes after nitroglycerine; blood pressure was 112/80. Note that the improvement in the ballistocardiogram is very marked.

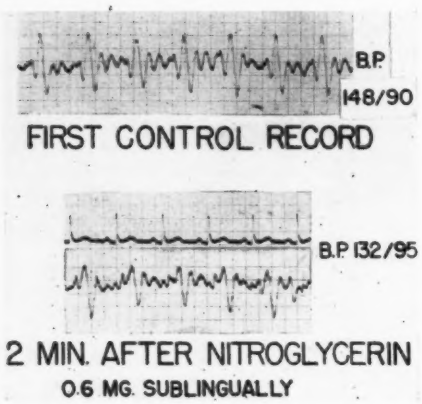


FIG. 5. Adverse effect of nitroglycerine. Subject R. A., male, Negro, aged 50, and weighing 175 pounds. Typical attacks of angina pectoris for the past two years. No history suggestive of cardiac infarction. Electrocardiogram, negative; heart, normal in size by x-ray films.

The control ballistocardiogram is normal, blood pressure at this time was 140/95 mm. Hg. The second record was taken two minutes after nitroglycerine. It is markedly abnormal, the J wave is greatly diminished and the I wave often does not reach the base line. The K wave is deep. Blood pressure was 132/95 mm. Hg at this time. In records taken 20 minutes later the normal form had been regained. This patient also showed marked deterioration of the ballistocardiogram after smoking one cigarette.

The rest of the hospital patients, those who could not be properly placed in any of the first three groups, were placed in a fourth group. These patients had little in common except the fact that neither coronary nor arteriosclerotic heart disease could be properly diagnosed by the usual clinical criteria. The primary diagnoses of these 51 cases included hyperthyroidism, diabetes mellitus, hypertension, peripheral vascular disease, chronic pericarditis, post pneumonectomy, former chest trauma, lymphatic leukemia, gastric ulcer, cirrhosis of the liver, recurrent pneumonia, diarrhea, hypercholesterolemia, rheumatic heart disease, polycythemia, chronic arthritis, and pelvic inflammatory disease. In addition we included in this group some elderly men who considered themselves to be in good health commensurate with their age. The healthy young adults, all medical students or recent graduates, were placed in the last group.

Needless to say the diagnosis of coronary heart disease or its absence cannot always be made with confidence during life. Especially when atypical chest pain is present, the propriety of assigning certain people to groups 1 or 4 might be long debated. We would have preferred that this decision be made without knowledge of the ballistocardiogram, but as we regularly reported our findings to the wards, this was not possible. To avoid bias, we have generally relied on the opinion of the clinician in charge; when the ward staff disagreed, we used our own judgment.

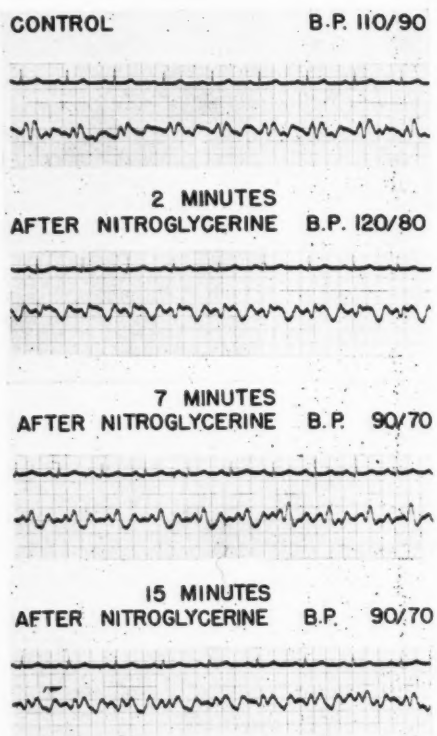


FIG. 6. A mixed effect after nitroglycerine. Subject D. L., aged 40, a woman. Formerly hypertension was present but under drug therapy the blood pressure had returned to normal. The control ballistocardiogram cannot be passed as altogether normal because H equals J in height in the smaller complexes. Two minutes after nitroglycerine the form is much more abnormal. J now exceeds H, and I is reduced to a notch on a plateau connecting J and H. However, five minutes later the record has changed its character; the I wave is too small but otherwise it is normal. The last record resembles the first, this shows that the effect of the drug has passed off.

TABLE 1.—*Ballistographic Response to Nitroglycerine in Various Clinical Conditions*

| Form of Original Ballisto | Change of Form After Nitroglycerine | Number of Persons Responding in Manner Indicated in Each of 5 Groups Diagnosed as Follows | | | | | Totals |
|---|---|---|---|---|---|---|---|
| | | Typical angina | Former cardiac infarction not followed by angina | Arteriosclerotic heart disease | All other patients | Healthy persons | |
| Normal | No change | 4 | 1 | | 18 | 18 | 41 |
| | Deteriorated | 4 | 1 | 1 | 4 | | 10 |
| Abnormal | No change | 10 | 1 | | 6 | | 17 |
| | Improved | 24 | 8 | 1 | 15 | | 48 |
| | Deteriorated | 8 | 4 | 1 | 2 | | 15 |
| | Mixed effects | | | | 3 | | 3 |
| Totals | | 50 | 15 | 3 | 48 | 18 | 134 |

Table 1 shows the frequency with which nitroglycerine caused improvement, deterioration or no noteworthy effect on the form of the ballistocardiograms of the patients classified as stated above.

We made no tests during the acute stage of cardiac infarction. By chance we made a test about 24 hours before such an attack and neither the ballistocardiogram nor the response to nitrites was found abnormal. A complete electrocardiographic study made at this time was also normal. The attack was a mild one and the patient made a good recovery.

## DISCUSSION

To those of the physiological school the reaction of the heart to a standard physiological test is of interest in itself, as it helps us to characterize and understand the physiological abnormalities encountered in our patients. So the work described in this paper was not undertaken with the primary aim of enabling doctors to make a descriptive diagnosis, such as angina pectoris, with greater confidence, though we would be glad if our work contributed to this end. Nor was the primary purpose of this study to enable doctors to increase their ability to make a pathological diagnosis, sclerosis of the coronary arteries, though we aim to learn all we can about the relationship between such lesions and the various aspects of cardiac performance. Let us, therefore, study these results for their own sake, always asking ourselves how the new knowledge can be used to the advantage of our patients.

That attacks of angina pectoris are accompanied by profound deterioration of the ballistocardiogram, is well established. Figures 1 and 2 give typical examples from our data; we have had four such cases. Others have secured similar results.[32] At the Second International Cardiological Congress,[15] Dr. Benjamin Baker showed a projection of a most abnormal record secured during such an attack; records secured before and after the attack were far more normal.

Kuo and Joyner[16] in a study of the effects of high blood fat, have obtained deteriorated ballistocardiograms during 14 attacks of angina. Dr. Raymond Penneys has similar records of one spontaneous attack, one induced by smoking, one induced by exercise and several induced by breathing a gas mixture low in oxygen.[17, 18] Indeed there is every reason to expect that the striking deterioration of the ballistocardiogram during anginal attacks would surely aid in distinguishing pain of cardiac origin from that arising elsewhere.

Nitrites have been given to many of these patients studied during an attack and, as the pain passed off, the ballistocardiogram improved. Also, Mandelbaum and Mandelbaum[19] subjected patients to a mild exercise test and evoked angina in two cases; ballistocardiograms, taken by the Dock method,[6] after nitroglycerine had brought relief, showed improvement over those taken before the exercise.

Therefore it seems well established that nitrites can bring about improvement in the abnormal ballistocardiogram found during attacks of angina pectoris.

In 84 per cent of the cases of angina pectoris tested in this study the ballistocardiogram was abnormal to some degree between attacks. That nitroglycerine, given although pain was absent, may favorably affect these records is evident from the results of this study; we found such an effect in 24 of our 42 cases of angina having abnormal records at rest, and in 8 of the 12 cases with a history of cardiac infraction not followed by angina. So it seems clear that an abnormality of myocardial function is present in these patients between attacks, and the fact that nitrites affected it favorably suggests that this abnormality has much in common with that present during an attack of angina, though doubtless it is less in degree.

One wonders if the cause of the improvement of our records after nitroglycerine is not related to the mechanism by which the drug relieves angina. For the latter, two possible mechanisms have long been known.[27] Nitrites might aid the heart by producing coronary vasodilatation similar to that so readily demonstrated in animal experiments,[31] and, as these drugs also lower blood pressure, they might relieve the heart by reducing its load. The sum total of these two effects would be reflected in the oxygen content of coronary venous blood, and Foltz and coworkers[28] have shown that, in animal experiments, the administration of nitrites is often followed by a marked increase in the oxygen content of coronary venous blood. Coronary vasodilators like aminophyllin, which stimulate the heart, do not have this effect, coronary venous blood oxygen often decreasing because the increased demand exceeds the increased supply.

Clinical studies on angina have, in general, supported the view derived from animal experiments. That increased blood pressure often occurs during angina has been known for many years,[27] so it has usually been presumed that increased cardiac work induces an attack, although blood pressure is only one factor in the heart's work. Indeed measurements of blood pressure, together with estimates of cardiac output made by an early cardiac output method, indicated that left ventricular work did increase during angina, and that this work diminished after nitroglycerine had relieved the pain.[20] On the other hand, Wayne and Laplace[21] studying the blood pressure during induced attacks of angina found that, while blood pressure regularly rose during attacks, there was no close correspondence between changes of blood pressure and the occurrence and relief of pain.

Our studies made between attacks likewise show no invariable correspondence between blood pressure and improvement in the ballistocardiogram, although this improvement was usually found while blood pressure was diminished. Thus our results show a few instances in which the record improved in the absence of a fall in blood pressure, some in which it regained its original abnormality while blood pressure remained down, and many cases in which a large diminution of blood pressure was not accompanied by any improvement in the record. In addition, the more rapid heart rate and the increased amplitude of the ballistocardiogram found after nitroglycerine in some of our records indicate that the heart's work per minute may not be diminished despite the lowering of blood pressure. Obviously, therefore, the available evidence does not permit us to attribute the improvement of the ballistocardiogram after nitroglycerine solely to diminution of heart work, although this may well be a factor in some cases; the coronary vasodilator action of that drug seems the more likely explanation for the improvement seen in most cases.

The 15 cases who gave no clear clinical evidence of coronary heart disease, but who had abnormal ballistocardiograms which improved after nitroglycerine, are of special interest. Of these, two belonged to the senior author's follow-up series and had been followed for 15 years. They were now 72 and 76 years of age, and the abnormality of their ballistocardiograms had developed in recent years. Both had been studied repeatedly at the hospital. The elder had an episode of precordial pain many years ago, judged by the attending physician to be due to cardiac infarction, but electrocardiographic confirmation had never been secured

and this diagnosis was doubted by subsequent cardiac consultants.

In several others chest pain was present but it was certainly not typical of angina. In J. F., a man aged 39, it had no relation to exertion and, routine studies being negative, it was attributed to anxiety. In M. K., a man of 55 (see fig. 4c), the pain was in the left arm and increased on walking, but hypertrophic arthritis of the spine was demonstrated, and the pain was relieved by supporting the arm by a bandage; so, routine cardiac studies being negative, the diagnosis of coronary heart disease was not entertained. E. S., a man of 68, had had attacks of abdominal pain and on one occasion it was referred to the chest; a renal calculus was discovered, as well as gas in the splenic flexure, and the pain was attributed to one or both of these. D. F., a woman of 37 with advanced rheumatic heart disease, complained of attacks of severe chest pain since she was 29. Aortic valvulotomy caused only temporary improvement. Nitroglycerine failed to relieve these attacks, but Demerol gave relief and she had become addicted to this drug. D. P., a woman of 68 with hypertension for many years, had had a stroke three years before and epilepsy since. She complained chiefly of epigastric pain relieved by alkalies; x-ray films showed a large hiatus hernia, and the pain was attributed to this. She had a large variety of other complaints among them a sense of pressure under the sternum, radiating "numbness" to both shoulders; this was precipitated by excitement but not by exercise. Her electrocardiogram revealed only non specific changes compatible with hypertension, and x-ray study disclosed only a minimal enlargement. In P. S. (see fig. 4) the pain was attributed to a demonstrated pulmonary lesion.

Chest pain was no feature in the other cases. P. R., a woman aged 52, had severe myxedema. A. D., a woman aged 48 was judged to have neurocirculatory asthenia based on anxiety. S. F., a man aged 57, came in for a routine check-up which was negative. J. B., a man of 48, had congenital hypercholesterolemia and was on a low fat diet. J. C., a man aged 52, was diagnosed duodenal ulcer; routine cardiovascular studies were negative. T. I., a woman aged 46, complained of nervousness, diarrhea, shortness of breath and of being "run down;" pain in the chest was denied, but she had right sided abdominal pain often relieved by alkalies. Her heart was negative to physical examination, other cardiac studies were not made; and the final diagnosis was cirrhosis of the liver. G. M., a woman aged 49, had advanced rheumatic heart disease, and she was tested just prior to commissurotomy.

Obviously, most of these patients were of an age at which coronary heart disease is found frequently at necropsy and some had symptoms that might have been attributed to that condition. Three had diseases, myxedema, congenital hypercholesterolemia and hypertension, in which coronary heart disease is a frequent complication. Two of the younger subjects had very severe rheumatic heart disease. The abnormal ballistocardiograms and the positive response to nitrolgycerine, if taken to indicate coronary heart disease, would come as a complete surprise only in a minority of the cases.

Dr. J. N. Morris, in a symposium on arteriosclerosis given at the Second World Congress of Cardiology, likened the incidence of coronary heart disease to a great pyramid of which, like a floating iceberg, only the apex was visible. According to this view the great majority of cases are not being detected during life by the clinical methods in common use. So it is certainly consistent with present knowledge to believe that the cases who have abnormal ballistocardiograms which improve after nitroglycerine belong to the submerged group whose abnormalities have not yet come to the surface and produced the familiar clinical pictures.

Proof of the presence of an anatomical lesion such as coronary arteriosclerosis can be obtained only at necropsy and our efforts to add to our knowledge by this means have continued. Our first case in which an abnormal ballistocardiogram was secured, while the subject believed himself to be in good health, has now been followed up to necropsy, and this seems an appropriate place to report it.

*Case Report*

C. N. was 48 years of age when his first ballistocardiogram was secured in 1937. He considered

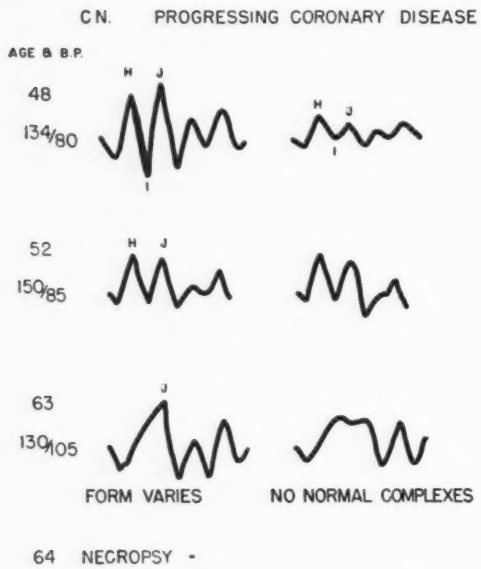


FIG. 7. Typical large and small complexes of a case of coronary heart disease followed for 16 years until necropsy. The three ballistocardiograms were all taken on the same instrument but by three different photographic techniques. The original records would be hard to compare by inexperienced readers. Therefore, atypical large and small complexes of the respiratory cycle have been selected from each record and drawn to scale above. The case history is in the text.

himself to be in excellent health and was leading a most active life as a medical teacher and investigator. Typical complexes from this first record are reproduced in figure 7, and they attracted our attention because the H wave so nearly equalled, or exceeded the J wave in height, and because of the low amplitude of the smallest complexes of the respiratory cycle.

This patient suffered from an attack of cardiac infarction in 1940 when aged 52. The symptoms and electrocardiographic changes were typical, the course was mild and he recovered sufficiently to pass all examinations for admission to the army and he served with distinction at a job requiring desk work in Washington during the war. Six months after the acute attack the second record of figure 7 was taken. The abnormality of the H wave was found to have increased, its height equalled or exceeded that of the J wave in all complexes.

Angina pectoris on severe exertion was noted following the acute attack and as years passed his exercise capacity diminished and he began to carry and take nitroglycerine. By 1953, dyspnea on exertion as well as pain were limiting facors, although he was still carrying on most effective work at a medical school. Under these circumstances the third record was taken. The ballistocardiogram was then extremely abnormal, no normal complexes were seen in any part of the respiratory cycle, the abnormality of form varied from beat to beat, the I wave, absent or very small, failed to reach the base line in many complexes, leaving the H and J waves fused.

After this, his condition deteriorated quite rapidly. X-ray examination demonstrated that the heart had enlarged. Attacks of paroxysmal atrial fibrillation began, also attacks of paroxysmal nocturnal dyspnea, but, except for occasional short stays at home, he continued to do effective work at a medical school until a few days before his death. He then went to Washington on business, where he had an unusually severe attack of angina and returned home. He had more pain at home but after a few days' rest seemed as well as usual. On the day of his death he arose feeling badly, collapsed and died before his physician arrived. Death took place almost exactly a year after the last ballistocardiogram.

At necropsy the pathologic lesions of importance were confined to the heart. There was severe coronary atherosclerosis with extreme narrowing of all branches. There was evidence of an old thrombotic occlusion (judged to be many years old) in the right coronary artery. The myocardium showed widespread severe damage, essentially subendocardial, but with two somewhat larger patches in the anterior and posterior walls. Of special interest were the extensive degenerative changes in the subendocardial region and the trabeculae of the left ventricle.

No definite acute muscle necrosis was present in the left ventricle though the variable staining in some areas was a bit suggestive. The finding of recent necrosis of muscle in the auricles was unexpected. No thrombi or recent obstructions were seen in any of the arteries.

The completed history of this case is certainly consistent with the view that coronary arteriosclerosis, found to such an advanced degree at necropsy was also present to some degree when the first abnormal ballistocardiogram was taken, although the subject certainly believed himself to be in good health at that time.

Let us now turn our attention to a more unexpected feature of our results, the fact that the drug, nitroglycerine, so widely used in coronary heart disease, caused temporary deterioration of the ballistocardiogram in a considerable proportion of our cases. This surprising finding has caused us to search for other evidence that drugs of this class might be cardiotoxic, and to examine the records of patients showing this

unexpected response in search of a clinical difference which might explain it.

In comparison with the 91 patients who did not show this effect the group of 25, whose records deteriorated after nitroglycerine were a little older, averaging 56.6 years against 52.7 years; and their blood pressure fell a little further, the average systolic fall being 16.9 mm. Hg in contrast to 14.4 mm. Hg, the average diastolic fall being 5.0 mm. Hg against 4.7 mm. Hg. There was a high percentage of persons with hypertension among those whose records became abnormal after nitroglycerine, 38 per cent having blood pressures higher than 150/100 mm. Hg, while only 23 per cent of the contrasting group were hypertensive. However, none of these differences is significant.

Of those showing deterioration of their records after nitroglycerine, 76 per cent had been diagnosed coronary or arteriosclerotic heart disease by the ordinary clinical criteria; obviously the great majority were coronary cases. Fifty-six per cent of the contrasting group were so diagnosed, a difference just failing to be significant.

Those whose records deteriorated after nitroglycerine and who were not diagnosed coronary heart disease included: L. S., a man of 54, found to have duodenal ulcer; M. D., a woman of 38, a complicated endocrine case suspected of acromegaly; R. W., a woman aged 33, and B. P., a woman of 74, both advanced cases of rheumatic heart disease; J. M., a man aged 50, suspected of hyperthyroidism; J. R., a man aged 34, who complained only of nervousness and a fainting spell; however, smoking a cigarette caused marked deterioration of his ballistocardiogram. Others were L. S., a woman aged 54, a former case of hyperthyroidism who came to the hospital for evaluation and whose basal metabolic rate was found normal; G. R., a man aged 67, who had moderate hypertension and cholelithiasis; and D. L. whose record is illustrated in figure 6. Obviously, several of those not diagnosed coronary or arteriosclerotic heart disease were of an age consistent with such a diagnosis and the remainder fall into no particular clinical group. Certainly, this analysis has not disclosed a clinical reason for the adverse effect of nitroglycerine and another explanation must be sought.

In animal experiments, nitrites do not always increase coronary flow. Text book statements concerning the conspicuous dilator action of nitroglycerine on the coronary circulation are derived chiefly from data secured from isolated heart preparations in which perfusion pressure is kept constant by the design of the experiment. In intact animal preparations, this effect on the coronary circulation is often far less striking, doubtless because the aortic pressure, which provides the perfusion pressure of the coronary arteries, so often falls after nitroglycerine. Thus in experiments on dogs, Eckenhoff and Hafkenschiel[29] found that nitroglycerine caused an increase in coronary flow only so long as the amount injected was not sufficient to produce a fall in blood pressure. These authors also observed instances in which coronary flow first increased, and then, as blood pressure fell, it decreased; so it is not hard to visualize how mixed or purely deleterious effects on the ballistocardiogram might be produced in man.

In addition, there are good reasons to expect differences between the action of drugs in healthy animals and in certain patients. It has been customary to think of the coronary circulation as a single physiologic unit; in the healthy, this is doubtless true. But when an arteriosclerotic heart is examined at necropsy, one has real doubts on this point. Uniform structural abnormality of the coronary tree is seldom, if ever, seen at necropsy. The lesions of arteriosclerosis are patchy in their distribution, stretches of normal vessel as well as areas of abnormality are found in the great majority of such cases. Especially if calcified, the advanced lesions make some parts of the coronary tree incapable of dilatation; certainly one cannot stretch many narrowed vessels to normal size with a probe. Such areas of rigidity might greatly alter the effect of a vasodilator, for, if some branches of the coronary tree are fixed, and others capable of responding, it seems that under many circumstances a drug causing dilatation would increase the blood flow within the dilated branch at the expense of the flow down the rigid branch, to the consequent im-

provement of the muscle function in one area of the heart, but to its detriment in another. We are inclined to explain the increased confusion of the ballistocardiogram seen in some of our subjects on this basis.

Stimulated by the adverse ballistic effects found in some of our patients, we have searched for clinical evidence of untoward effects of nitrites. Prodger and Ayman[23] described alarming reactions to nitroglycerine in 4 of 110 patients who had received the same doses we used, or double that dose. These reactions were characterized by a profound fall in blood pressure in two cases, heart block in one, marked slowing of the pulse in two, accompanied by weakness, sweating, nausea and faintness. But in most respects, the untoward effects described by Prodger and Ayman resemble the usual syncopal reaction, such as might attack any person in the upright position during the action of any vasodilator drug; and except for the development of heart block in one case, this experience provides no conclusive evidence that nitrites are cardiotoxic.

At the Second World Congress of Cardiology, where our preliminary report was also given, Russek and coworkers[24] reported that 15 of 158 patients with coronary heart disease, when given nitroglycerine before a standard exercise test, developed greater abnormalities of the electrocardiogram than were present in control records, and these authors concluded that this drug has latent potentialities for adverse effects. Others have told us that they also have seen adverse changes in the electrocardiogram after nitroglycerine, but they did not consider them important. In our experiments the simultaneous electrocardiogram did not show any change when the ballistocardiogram deteriorated after nitroglycerine.

So the clinical evidence that nitrites, as given to patients, can produce real harm to the heart seems to us to be extremely meagre. Nitrites do not produce angina, although often given to patients subject to this disorder. We have no wish to emphasize unduly the importance of our findings; the effect judged to be adverse was fleeting, and our subjects had no complaints at this time. Indeed we would have been inclined to dismiss these findings as unimportant had it not been for recent evidence indicating that nitrites may have toxic potentialities far greater than has been realized.

Suspicions of cardiac toxicity of a much more serious sort have been directed at nitroglycol, a volatile nitrite not used in medicine, but identified as a hazard to those engaged in the manufacture of explosives in Europe during the last war. This deserves the attention of doctors because nitroglycol produces effects on the human body very similar to, if not identical with, those of nitroglycerine.[22] The cases reported by Gross[25] occurred in workers in the explosive industry who were not elderly and who had previously been in good health. The persons affected collapsed suddenly and there were some fatalities. It is remarkable that the collapse never occurred while they were at work but took place several days after cessation of exposure, as on Sunday night or Monday morning. Writing 10 years later, Symanski[26] collected 49 fatal accidents of the same kind in workers exposed to nitroglycol and reported three cases he had seen himself. Previously in good health, these workers collapsed suddenly usually during moderate exertion as while walking to work. Symanski found low blood pressure, abnormal pulse rate and electrocardiographic abnormalities during the last illness. Necropsy performed in three cases did not disclose any anatomic abnormality to which death could be attributed, so the exposure to nitroglycol was implicated.

We know of no evidence to indicate that serious cardiotoxic effects, such as those attributed to industrial exposure to nitroglycol, ever occur in patients given nitroglycerine by their physicians. Needless to say, many cases of angina taking nitroglycerine have suffered sudden death, but the tendency of such cases to "fall down and perish almost immediately" was recognized by Heberden many years before the first use of nitrites in this disease by Lauder Brunton.

Nevertheless it is sobering to reflect that, should the nitrites be playing a role in such unhappy accidents, this would almost certainly be overlooked by the physician in charge, for death would be attributed to the underlying disease. For this reason, the increasing evi-

dence that nitrites, used with such great benefit to most cases of angina, may disturb cardiac function under certain circumstances, must be kept in mind by the profession.

In conclusion, it is interesting to consider a possible interpretation of the adverse ballistocardiographic changes after nitroglycerine which can be tested by our results. In the majority of our patients showing such effects, coronary heart disease had been diagnosed, and so it is likely that coronary sclerosis was present. If the whole or a considerable part of the coronary arteries had become narrowed, and so rigid that dilatation was impossible, the action of nitrites by causing a fall in blood pressure in the root of the aorta, would diminish blood flow in the area supplied by the rigid vessels, since the aortic pressure provides such a large part of the driving force of the coronary circulation. So if the development and retrogression of increased ballistic abnormality after nitroglycerine coincided with the fall and rise of aortic pressure, it would suggest that the coronary sclerosis was especially severe. Most of our results are consistent with this attractive theory, for, as a rule, the blood pressure was reduced during the period of increased ballistic abnormality. But a few of our results are not consistent with this view. We have encountered instances during a period of increased ballistic abnormality after nitroglycerine, when the arterial pressures were as high or higher than during the control period. This was most often seen during recovery from the effects of the drug. We are, therefore, driven to the view that other factors must enter into the adverse effects in some cases. But whatever the complete explanation, the fact that the usual dose of nitroglycerine, though more often causing marked improvement of cardiac function, may also cause deterioration of cardiac performance, should be kept in mind by doctors prescribing it.

## Conclusion

The effect of nitroglycerine on the ballistocardiogram has been studied in 18 healthy young adults and in 116 patients, 63 of whom had been diagnosed as having coronary or arteriosclerotic heart disease from the usual clinical evidence. Nitroglycerine had no effect on the form of the record of healthy young adults.

The ballistocardiogram deteriorated markedly during two attacks of angina pectoris. When given nitrites, as pain was relieved, the form of the ballistocardiogram improved greatly.

Most of our patients suffering from angina pectoris gave abnormal ballistocardiograms when tested between attacks. When given nitroglycerine, their records improved temporarily in about one-half of the cases tested. So the action of nitrites may bring about improvement in the record when given both during and between attacks of angina pectoris.

In patients who had had cardiac infarction not followed by angina pectoris, abnormal ballistocardiograms were improved temporarily by nitroglycerine in over half of the cases.

Patients in the latter half of life who have abnormal ballistocardiograms, but no history of angina pectoris, and no clinical evidence of coronary heart disease, showed temporary improvement in their records after nitroglycerine in two-thirds of the cases, a finding consistent with the view that they actually suffered from coronary heart disease of a form or to a degree not yet clinically manifest.

A case is reported in which an abnormal ballistocardiogram was secured while the subject believed himself to be in good health; later cardiac infarction developed, and still later advanced coronary arteriosclerosis was found at necropsy.

Despite the frequency with which improvement of the ballistocardiogram is seen after nitroglycerine, temporary deterioration of this record may follow the action of this drug when it is given in the dosage commonly employed by physicians.

The possible physiologic meaning of these untoward effects is discussed and attention is called to new evidence of serious toxic effects including collapse and sudden death, encountered in certain European workers exposed to a volatile nitrite during the manufacture of explosives.

### Summarío in Interlingua

Nitroglycerina esseva administrate a un serie de patientes, e su effecto super le ballistocardiogramma esseva observate. Attaccos de angina de pectore es accompaniate de un forte deterioration del registration: si alora nitroglycerina es administrate le registration se meliora quando le dolores subside. Administrate inter attaccos, a patientes de morbo cardiac coronari con ballistocardiogrammas anormal, nitroglycerina es grequentemente sequite per un melioration del registration. Le mesmo es ver quando nitroglycerina es administrate a patientes de etates plus avantiate qui ha ballistocardiogrammas anormal sed nulle signo clinic de morbo cardiac coronari. Iste facto concorda con le these que morbo cardiac coronari es presente in tal casos. Del altere latere, nitroglycerina es a vices sequite de un deterioration del ballistocardiogramma. Le rationes possibile de iste inexpectate constatation es discutite. Es signalate recente datos que indica que serie effectos toxic pote sequer le exposition al effecto de nitritos in uso industrial.



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# The Electrocardiogram in Congenital Heart Disease

## With Special Reference to Left Axis Deviation

*By* A. J. Brink, M.D., (Pretoria), M.R.C.P. (Lond.) and Catherine A. Neill, M.D., M.R.C.P. (Lond.)

The incidence of the four main types of axis deviation in each diagnostic group of congenital malformations of the heart was found by an examination of 2,752 electrocardiograms from the Harriet Lane Home Cardiac Clinic. Records from patients with dextrocardia or dextrarotation of the heart, and those with complete bundle branch block were excluded. The precordial and unipolar limb leads in the 289 electrocardiograms which showed left axis deviation were examined, and the types of precordial pattern most frequently seen in the different diagnostic groups analyzed. It is concluded that the precordial patterns show considerable difference in the various malformations associated with left axis deviation, and are of diagnostic aid.

THE FREQUENT FINDING of left axis deviation in the electrocardiogram of patients with tricuspid atresia and its extraordinary rarity in other cyanotic cardiac malformations, prompted an investigation into the degree of deviation of the electrical axis of the heart in congenital heart disease.

A total of 2,874 electrocardiographic records was studied from different patients who attended the Harriet Lane Home Cardiac Clinic between 1946 and 1952. Only patients with congenital malformations of the heart are included; cases of functional murmur or acquired heart disease were omitted. The electrocardiogram described is that obtained at the first attendance. Among the 2,874 records, there were 77 instances of dextrocardia or dextrorotation of the heart and 45 instances of complete bundle branch block; eight of these showed a Wolff-Parkinson-White syndrome, three left bundle branch block and 34 right bundle branch block. All of these were excluded from the study, leaving a total of 2,752 electrocardiograms from patients with congenital heart disease.

*The clinical diagnosis* in each case was based on a complete medical history, physical examination, fluoroscopy, and x-ray films of the heart. A red blood cell count, hemoglobin and hematocrit was obtained. Many patients were subsequently re-examined and cardiac catheterization and angiocardiography performed.

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Dr. Brink is a C. J. Adams and C.S.I.R. Travelling Fellow, South Africa, 1951–1952.

It should be emphasized that a large number of patients referred to this clinic, particularly in 1946 and 1947, were in the cyanotic group; 845 of the 2,752 records were from patients with tetralogy of Fallot. For this reason, this study cannot be used to determine the incidence of the various malformations in congenital heart disease. It is believed, however, that within each diagnostic group, the incidence of the four main types of axis deviation can be assessed and is significant.

The findings in the present series are considered in two parts. Part I is devoted to the incidence of the different types of axis deviation in this series of cases, and Part II to a detailed analysis of the electrocardiograms showing left axis deviation.

### Part I.—The Incidence of the Different Types of Axis Deviation in Various Congenital Malformations

The Criteria Committee of the New York Heart Association[1] has adopted three simple descriptive groups for the electrical axis of QRS. These are: no deviation of the electrical axis, 30 to 90 degrees; left deviation of the electrical axis, 29 to minus 90 degrees; right deviation of the electrical axis, 91 to minus 91 degrees. This nomenclature has been adopted

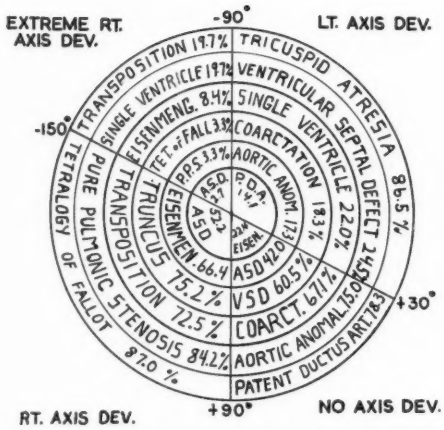


FIG. 1. The four main types of axis deviation, and the six congenital malformations most commonly associated with each type.

in this paper with a slight modification. The group of right axis deviation has been divided into: right deviation of the electrical axis, 91 to minus 149 degrees; an extreme right deviation of the electrical axis, minus 150 to minus 91 degrees.

(1) No axis deviation (plus 90 to plus 30 degrees) was present in 34.5 per cent of all cases (944 records).

(2) Left axis deviation (plus 29 to minus 90 degrees) was present in 10.5 per cent of all cases (289 records).

(3) Right axis deviation (plus 91 to minus 149 degrees) was present in 51.1 per cent of all cases (1,411 records).

(4) Extreme right axis deviation (minus 91 to minus 150 degrees) was present in 3.9 per cent of all cases (108 records).

The high incidence of right axis deviation in this series probably reflects the large number of cyanotic patients seen. The least common type of axis deviation is that lying between minus 90 and minus 150 degrees. In figure 1, the four types of axis deviation are represented as segments of a circle, and the six most common malformations in each type are shown.

*Right axis deviation* was present in 87 per cent of the 845 patients with tetralogy of Fallot, in 84 per cent of the 177 with pulmonary valvular stenosis, and in 75 per cent of the 85 patients with truncus arteriosus. The incidence of right axis deviation in auricular septal defect, Eisenmenger's complex, and transposition of the great vessels ranged between 50 and 70 per cent. The incidence in ventricular septal defect and in coarctation of the aorta was 15 per cent; indeed, the majority of infants under 2 years of age with coarctation showed right axis deviation. In figure 2, the total number of patients with each clinical diagnosis is shown and the incidence of each type of axis deviation, in that diagnostic group, is reported.

*No axis deviation* was present in approximately 70 per cent of patients with patent ductus arteriosus, congenital aortic valvular lesions, or coarctation of the aorta. Isolated ventricular septal defect was diagnosed in 348 patients, 60 per cent of whom showed a normal axis. There were 224 patients with

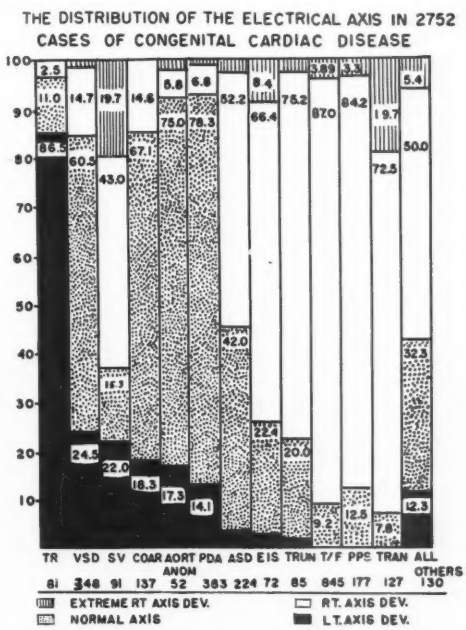


FIG. 2. The distribution of the electrical axis in 2,752 cases of congenital heart disease. (Total cases in each group is given below diagnosis.) *Abbreviations:* TR, tricuspid atresia. VSD, ventricular septal defect. SV, single ventricle. COAR, coarctation of the aorta. AORT ANOM, other aortic anomalies. PDA, patent ductus arteriosus. ASD, auricular septal defect. EIS, Eisenmenger's complex. TRUN, truncus arteriosus. T/F, tetralogy of Fallot. PPS, pulmonary valvular stenosis. TRAN, transposition of the great vessels.

auricular septal defects, 42 per cent with a normal axis. In Eisenmenger's complex and truncus arteriosus, the incidence of normal axis deviation was approximately 20 per cent; in tetralogy of Fallot, pulmonary valvular stenosis, transposition of the great vessels and tricuspid atresia, it was approximately 10 per cent.

*Extreme right axis deviation* was most often observed in transposition of the great vessels and in single ventricle (20 per cent of 127 cases and 91 cases, respectively). The incidence in Eisenmenger's complex was 8 per cent, and in tetralogy of Fallot and auricular septal defect approximately 3 per cent. It was not seen in tricuspid atresia.

*Left axis deviation* was present in 289 instances. A diagnosis of tricuspid atresia was made in 70 of these patients and confirmed at autopsy in 11. Left axis deviation thus occurred in 86 per cent of the 81 patients with this diagnosis. Of the 348 patients with ventricular septal defects, 84 (24 per cent) showed left axis deviation. The clinical diagnosis was confirmed by cardiac catheterization in 11 of the 84. Single ventricle was diagnosed in 91 patients of whom 20 (22 per cent) showed left axis deviation. The diagnosis was confirmed at autopsy in only 6. Coarctation of the aorta was present in 137 patients, of whom 24 (18 per cent) showed left axis deviation: in 16 of these, the diagnosis was confirmed at operation. The diagnostic group "other aortic anomalies" includes 52 patients with congenital aortic or subaortic stenosis, vascular ring, or congenital aortic insufficiency. Of these, 9 (17 per cent) showed left axis deviation. Only 54 patients (14 per cent) with a patent ductus showed left axis deviation; the diagnosis was confirmed surgically in 43.

There were 28 patients with left axis deviation not included in the six major diagnostic groups above. Of these, seven had auricular septal defects (two confirmed by cardiac catheterization).* There were also two patients with Eisenmenger's complex and two with truncus arteriosus (which represented an incidence of left axis deviation of 2.5 per cent in both these conditions).

The 17 remaining cases are included in the group of "rare malformations" shown in the last column of figure 2. There were 6 patients, out of a total of 19 patients, with situs inversus and levocardia in whom the electrocardiogram showed left axis deviation. One of the six came to autopsy and had a single ventricle and a large auricular defect. The diagnosis of atrioventricularis communis was made in 12 instances (mainly on the basis of coexisting mongolism), and in four of these left axis deviation was present. Left axis deviation was seen in one instance in each of the following diagnostic groups: Ebstein's anomaly (total 14 cases), congenital mitral insufficiency (total five cases), pulmonary hypertension with reversed flow through a patent ductus (total six cases), and underdevelopment of the right ventricle without tricuspid atresia (total three cases). Cardiomegaly of undetermined origin was associated with left axis deviation in three patients.

Among the electrocardiograms in this study, no instance was found of left axis deviation in association with tetralogy of Fallot, pulmonary valvular stenosis, or transposition of the great vessels. Since the data were collected, however, one infant with marked left axis deviation was found to have complete transposition and a small right ventricle at autopsy.

Confirmation of the clinical diagnosis in the 289 cases showing left axis deviation, was obtained in only slightly over one-third of the cases. In 20, the diagnosis was confirmed by autopsy, in 59, by surgery, and in 34 by cardiac catheterization or angiocardiography, or both.

## Part II.—Analysis of Electrocardiograms with Left Axis Deviation

A marked degree of left axis deviation (minus 31 to minus 90 degrees) was more frequent in single ventricle and tricuspid atresia than in the other malformations. In patent ductus arteriosus, coarctation of the aorta, and other aortic anomalies, left axis deviation was frequently mild and seldom more than moderate in degree (table 1).

The 289 records which showed left axis

* It has been the experience of this clinic, that in this malformation left axis deviation usually indicates a low septal defect of the ostium primum type.

TABLE 1.—*The Electrical Axis Within the Six Major Groups of Congenital Heart Disease Showing Left Axis Deviation*

| Diagnosis | No. cases | Slight l. axis, +29° to 0° | Moderate, −1° to −30° | Marked l. axis, −31° to −90° |
|---|---|---|---|---|
| | | % | % | % |
| Tricuspid atresia | 70 | 9 | 25 | 66 |
| Single ventricle | 20 | 15 | 10 | 75 |
| Vent. septal defect | 84 | 37 | 31 | 32 |
| Pat. duct. art. | 54 | 59 | 26 | 15 |
| Coarctation | 24 | 42 | 46 | 12 |
| Aort. anom. | 9 | 55 | 45 | 0 |
| Total | 261 | 37 | 30 | 33 |

deviation were further analysed to determine what differences, if any, were present in the precordial and unipolar limb leads in the various diagnostic groups, and whether left axis deviation was uniformly accompanied by other evidence of left ventricular preponderance.

*Unipolar Limb Leads in Cases with Left Axis Deviation*

The augmented limb leads of Goldberger[2] $aV_R$, $aV_L$ and $aV_F$ had been taken in 157 patients with left axis deviation in the electrocardiogram. These leads were studied only to determine the electrical position of the heart in relation to the antero-posterior axis of the body. The position was horizontal or semi-horizontal in 146 of the 157 cases.

*Precordial Leads in Cases with Left Axis Deviation*

Precordial leads were taken in 278 of the 289 patients with left axis deviation. A right and left precordial lead ($V_1$ and $V_5$ or $V_6$) were used for analysis and the pattern in each was classified according to the scheme set out in figure 3. The total number of cases in each clinical group with a particular type of precordial pattern is shown in figure 4. The patterns in the precordial leads give reliable information concerning the relative thickness of right and left ventricle. In this sense the term "preponderance" of one ventricle over the other has been used in the interpretation of these leads. Such preponderance may be normal and the term is not used to indicate hypertrophy.

*Type I (R Pattern).* The prominent R wave may be preceded by a Q or followed by an S wave, or both may be present. The R wave may be slurred but not notched and the duration of the whole complex is less than 0.10 second. When this pattern occurs in $V_1$, it is taken to indicate right ventricular preponderance (fig. 3, $V_1$ type I). An S wave is usually present in this lead in the physiological type of right ventricular preponderance seen in infancy. Consequently in this age group Rs pattern is frequent but R or qR is rare, and when it does occur, is usually associated with pathological right ventricular hypertrophy. Only 30 instances of this $V_1$ type I pattern were found in the electrocardiograms showing left axis deviation, and subdivision into physiological and pathological patterns was not attempted.

An R or qR pattern in $V_5$ which is the pattern of normal preponderance, was found in 224 records (fig. 4).

*Type II a. ($rSr_1$ Pattern).* The r and $r_1$ are of equal amplitude and the duration of the whole complex less than 0.11 second. This pattern in $V_1$ is generally considered normal in children.[3, 4]

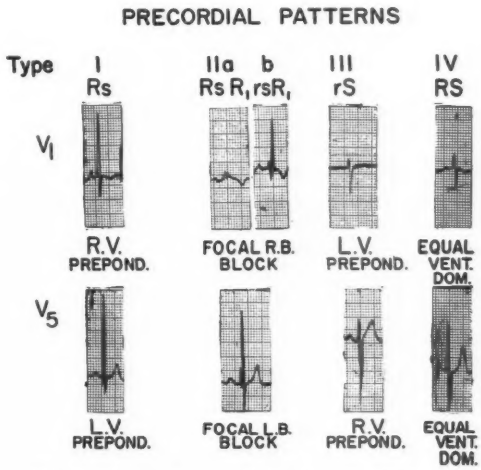


FIG. 3. Types of precordial pattern. *Abbreviations:* RV, right ventricle. LV, left ventricle. PREPOND., preponderance. VENT. DOM., ventricular dominance.

| DIAGNOSIS / AGE | No. of cases | $V_1$ pattern Type | I | IIA | IIB | III | IV | $V_5$ or $V_6$ pattern I | II | III | IV |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TRICUSPID ATRESIA | 66 | | | | | 59 | | 55 | | | |
| 0-6 mo. | 13 | | | | | 10 | 3 | 11 | | 1 | 1 |
| 6-12 " | 12 | | | | | 11 | 1 | 9 | | 2 | 1 |
| 1-2 yr. | 6 | | | | | 6 | | 5 | | 1 | |
| 2-5 " | 11 | | | | | 10 | 1 | 9 | | 2 | |
| 5-15 " | 20 | | | | | 18 | 2 | 17 | | 1 | 2 |
| 15 yrs. + | 4 | | | | | 4 | | 4 | | | |
| SINGLE VENTRICLE | 19 | | | | | 12 | | 11 | | | |
| 0-6 mo. | 3 | | 1 | | | 2 | | | | 1 | 2 |
| 6-12 " | 4 | | | | 3 | | 1 | 2 | | 1 | 1 |
| 1-2 yr. | 3 | | 1 | | | 2 | | 3 | | | |
| 2-5 " | 2 | | 1 | | | 1 | | 1 | | | 1 |
| 5-15 yr. | 4 | | | | | 4 | | 2 | | 1 | 1 |
| 15 yrs. + | 3 | | | | | 3 | | 3 | | | |
| VENT. SEPT.DEFECT | 82 | | | | | 32 | | 63 | | | |
| 0-6 mo. | 11 | | 5 | | 3 | 3 | | 9 | | | 2 |
| 6-12 " | 7 | | 5 | | 1 | 1 | | 4 | | 1 | 2 |
| 1-2 yr. | 14 | | 2 | 2 | 4 | 4 | 2 | 11 | | | 3 |
| 2-5 " | 20 | | 2 | 4 | | 11 | 3 | 14 | | | 6 |
| 5-15" | 24 | | 1 | 4 | 8 | 11 | | 19 | | 1 | 3 |
| 15 yrs. + | 6 | | 1 | 3 | | 2 | | 6 | | | |
| PAT.DUCT. ART. | 52 | | | | | 31 | | 50 | | | |
| 0-6 mo. | 3 | | 1 | | | 1 | 1 | 2 | | | 1 |
| 6-12 " | 1 | | | | | | 1 | 1 | | | |
| 1-2 yr. | 5 | | 1 | 2 | | | 2 | 5 | | | |
| 2-5 " | 10 | | 2 | | | 4 | 4 | 9 | | 1 | |
| 5-15 " | 22 | | 1 | | 1 | 16 | 4 | 22 | | | |
| 15 yrs. + | 11 | | | | | 10 | 1 | 11 | | | |
| COARCTATION | 24 | | | | | 19 | | 18 | | | |
| 0-6 mo. | 0 | | | | | | | | | | |
| 6-12 " | 0 | | | | | | | | | | |
| 1-2 yr. | 1 | | | 1 | | | | | | 1 | |
| 2-5 " | 2 | | | 1 | 1 | | | | | | 2 |
| 5-15 " | 11 | | | 1 | 1 | 9 | | 9 | | | 2 |
| 15 yrs. + | 10 | | | | | 10 | | 9 | | | 1 |
| RARER GROUPS | 35 | | | | | 16 | | 27 | | | |
| AORTIC LESIONS | 9 | | | | | 9 | | 9 | | | |
| AURICULAR DEFECT | 7 | | 1 | 3 | 3 | | | 3 | | 1 | 3 |
| SITUS INV.& LEVO. | 6 | | 2 | | 1 | 3 | | 4 | | 1 | 1 |
| A.V.COMMUNIS | 4 | | 1 | | | 2 | 1 | 3 | | | 1 |
| EISENMENGER | 2 | | 1 | 1 | | | | 2 | | | |
| TRUNCUS | 2 | | | | 1 | | 1 | 2 | | | |
| UNDER DEV. R.V. | 1 | | | | | 1 | | 1 | | | |
| REVERSED DUCTUS | 1 | | | | 1 | | | | | 1 | |
| EBSTEIN'S | 1 | | | | 1 | | | 1 | | | |
| CARDIOMEG. ? CAUSE | 2 | | | | 1 | 1 | | 2 | | | |

FIG. 4. The distribution of the different types of precordial patterns in patients with congenital heart disease with left axis deviations, showing 243 cases. There are 5 major diagnostic groups, subdivided by age; also 35 cases in the rarer diagnostic groups.

*Type II b.* (*$rSR_1$ Pattern*). The $R_1$ is of greater amplitude than the initial R. The total is less than 0.11 second. Some authors[5, 6] consider that this type II b pattern in $V_1$ is usually associated with right ventricular hypertrophy.

In the present series, $V_1$ type II (a and b) occurred 51 times and was most frequent in children over 1 year of age with ventricular septal defects, auricular septal defects and coarctation. The pattern was not seen in tricuspid atresia.

No instances of $V_5$ type II pattern, indicative of incomplete left bundle branch block, were found in the present series.

*Type III* (*rS Pattern*). There is a small positive R deflection followed by a large negative S wave and the total duration of the complex is less than 0.10 second. This pattern in $V_1$ is seen in normal adults and with increasing frequency in normal children as age advances. It reflects the normal left ventricular preponderance and occurred in 169 instances in the present series. In most malformations, the incidence was greater in the older age groups but in tricuspid atresia it was almost invariably present from birth (fig. 4).

The rS pattern in $V_5$, which may mean right ventricular preponderance was seen in only 17 cases in the present series.

*Type IV (RS Pattern).* The R wave and S wave are of equal amplitude. In $V_1$ it was seen in 28 instances in the present series, including 14 of the 52 patients with patent ductus arteriosus, and all seven cases of tricuspid atresia in which a $V_1$ Type III pattern was not present.

An RS pattern in $V_5$ was present in 36 instances, that is, in the majority of records which did not show the R pattern in this lead.

*Correlation of the Type of Precordial Pattern in $V_1$ and $V_5$.* Patients with congenital heart disease, who showed left axis deviation in the electrocardiogram, had a type I pattern in $V_5$ in 81 per cent of cases (224 of 277 records). This pattern of left ventricular preponderance was not noticeably influenced by age. The incidence of a left ventricular preponderant pattern in $V_1$ was lower (61 per cent); furthermore, in most malformations it was more common in the older age group.

A left ventricular preponderant pattern in both $V_1$ and $V_5$ occurred in 83 per cent of patients with tricuspid atresia, and did not vary with age. This combination was found in all cases of "other aortic anomalies" with left axis deviation and, in 75 per cent of those with coarctation, 58 per cent of those with patent ductus and 42 per cent of the 19 cases of single ventricle.

The combination of a type I pattern in $V_5$ and type IIa or IIb pattern (incomplete right bundle branch block) in $V_1$ occurred in 45 per cent of cases of ventricular septal defect, and in 20 per cent of the patients under 15 years with a patent ductus. This combination has come to be considered very typical of these two conditions; it is also frequently found in these malformations even when there is no deviation of the electrical axis.

An rS pattern, which when seen in $V_1$ indicates left ventricular preponderance and in $V_5$ indicates right ventricular preponderance, was seen in both leads only in tricuspid atresia and single ventricle. It is believed that, at least in the former condition, it indicates clockwise rotation of the heart.

A type IV pattern in both $V_1$ and $V_5$ was seen occasionally in tricuspid atresia and in ventricular septal defect.

## Discussion

The nomenclature adopted for the electrical axis of QRS is descriptive and does not indicate which of the subdivisions are normal or abnormal.

The presence of left axis deviation in children and even in youth may be of some significance. In a study of 1,276 electrocardiograms taken in 167 average healthy infants and children whose ages ranged from 3 weeks to 12 years, 4.73 per cent were found to have left axis deviation.[7] The criteria for axis deviation was similar to that used in this study. In another series of 679 healthy infants and children ranging in age from 6 months to 9 years, only three were found with an electrical axis less than 0 degrees.[8] A further study of 100 healthy children aged between a few weeks and 14 years, only two were found to have an electrical axis less than 20 degrees.[9] Even in normal young adults left axis deviation is not a common finding; in a study of 500 young adult males no more than 22 were found to have axes less than 0 degrees.[10]

Little uniformity has been present in the criteria adopted for the description of axis deviation in these reports on normal individuals. In the present series of patients, 845 had tetralogy of Fallot; the right axis deviation, which occurs so frequently in this condition, would decrease the incidence of left axis deviation in the group as a whole. Also, this series of patients with congenital heart disease, although very largely composed of infants and children does contain a small number of young adults. For these reasons the true significance of left axis deviation in the electrocardiograms of children is difficult to assess. Nevertheless, the incidence of 10.5 per cent of children with left axis deviation in this series of 2,786 patients with congenital heart disease suggests that this finding is frequently associated with an abnormality and therefore whenever found warrants further investigation before the child is considered normal.

In this large group of congenital cardiac

conditions, it appears furthermore that with very few exceptions those conditions where left ventricular preponderance is expected are either in the left axis deviation group or the no axis deviation group. Those conditions with right ventricular preponderance are to be found in the right axis and extreme right axis groups.

Analysis of the precordial and limb leads in the electrocardiograms which showed left axis deviation, reveals that in tricuspid atresia and in some instances of single ventricle, there is definite associated left ventricular preponderance. These two conditions account for the great majority of patients with cyanotic congenital heart disease who show left axis deviation. More rarely, this combination of left axis deviation and cyanosis may be seen in Eisenmenger's complex, truncus arteriosus, situs inversus with levocardia, atrioventricularis communis, or underdevelopment of the right ventricle without tricuspid atresia. The precordial electrocardiograms in these conditions may show right ventricular preponderance, incomplete right bundle branch block, or equiphasic QRS complexes over the precordium indicative of equal dominance of the two ventricles.

In acyanotic patients, left axis deviation is not so markedly limited to a single malformation. It is found with varying frequency in patients with ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, and other aortic anomalies. In patients with aortic anomalies, the precordial leads reveal that left axis deviation is uniformly accompanied by left ventricular preponderance. In other malformations, left axis deviation is frequently associated with a left ventricular preponderant pattern in $V_5$: in ventricular septal defect and patent ductus in early childhood this pattern may be accompanied by incomplete right bundle branch block in $V_1$, or even a right ventricular preponderant pattern in this lead.

## Summary

The electrocardiograms of 2,752 patients with congenital malformations of the heart were examined and divided into four groups: (1) No axis deviation (34.5 per cent); (2) left axis deviation (10.5 per cent); (3) those with right axis deviation (51.1 per cent) and (4) extreme right axis deviation (3.9 per cent). Electrocardiograms from patients with dextrorotated hearts or complete bundle branch block were excluded. Right axis deviation occurred in all the malformations studied but was most frequent in pulmonary valvular stenosis and tetralogy of Fallot.

No axis deviation was found also in association with all the malformations studied; it was seen most frequently in patent ductus, coarctation of the aorta, other aortic anomalies, and ventricular septal defects. Extreme right axis deviation was rare and occurred more frequently in transposition of the great vessels and in single ventricle than in other anomalies. It was not seen in tricuspid atresia or coarctation of the aorta. Left axis deviation in cyanotic patients was overwhelmingly associated with tricuspid atresia although it was seen in single ventricle, Eisenmenger's complex, truncus arteriosus, and a few rare anomalies. In this series, it was not seen in tetralogy of Fallot, pulmonary valvular stenosis or transposition of the great vessels. Among acyanotic patients, left axis deviation was most frequent in ventricular septal defects, coarctation of the aorta, other aortic anomalies and patent ductus arteriosus.

Unipolar limb leads were available in 157 of the 289 electrocardiograms which showed left axis deviation. In 146 of these the electrical position was horizontal or semihorizontal.

The precordial electrocardiogram was available for analysis in 278 of the 289 cases which showed left axis deviation. Among cyanotic patients, left axis deviation was accompanied by marked evidence of left ventricular preponderance in tricuspid atresia and some cases of single ventricle; more variable patterns were obtained in the other malformations. Among acyanotic patients, definite left ventricular preponderance was seen in association with aortic anomalies. In infancy and early childhood, a pattern of left ventricular preponderance in $V_5$ and incomplete right bundle branch block in $V_1$ was a frequent combination in patients with ventricular septal defect,

patent ductus arteriosus, and occasionally coarctation of the aorta.

### Acknowledgments

We should like to acknowledge with gratitude the constant help and encouragement of Dr. Helen B. Taussig, without whom this study would have been impossible. We should also like to thank Mrs. V. Rogers, Mrs. M. Lindermann, and Mrs. P. Schaff for their technical assistance.

### Summario in Interlingua

Le frequentia del quatro major typos de deviation axial in cata gruppo diagnostic de congenite malformationes del corde esseva determinate per le examine de 2.752 electrocardiogrammas obtenite al Clinica Cardiac del Harriet Lane Home a Baltimore, Md. Esseva excludite le registrationes ab patientes con dexterocardia o dexterorotation del corde e con complete bloco del branca dextere. Le derivationes precordial e unipolar extremital esseva examinate in le 289 electrocardiogrammas exhibiente deviation sinistrorse del axe. Le typos del configurationes precordial que esseva incontrate le plus frequentemente in le varie gruppos diagnostic esseva analysate. Nos conclude que le configurationes precordial monstra considerabile differentias in le varie malformationes associate con deviation sinistrorse del axe e que assi illos pote esser de adjuta diagnostic.

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# Left Axis Deviation in Tricuspid Atresia and Single Ventricle

## The Electrocardiogram in 36 Autopsied Cases

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The electrocardiograms from 28 unselected autopsied cases of tricuspid atresia, and eight autopsied cases of single ventricle were analysed: only those cases of single ventricle which showed left axis deviation were included. Electrocardiographic evidence of left ventricular preponderance in the precordial and unipolar limb leads was found in 27 of the 28 cases of tricuspid atresia, and three of the eight of single ventricle: In only two cases of single ventricle was the electrocardiogram identical with that seen in tricuspid atresia, and in one of them tricuspid stenosis was present. Right auricular hypertrophy as evidenced by high peaked P waves, together with presystolic hepatic pulsations occurred in tricuspid atresia in those instances in which, at autopsy, the interauricular communication was found to be small.

THE FINDING of left axis deviation in a cyanotic child is very suggestive of tricuspid atresia.[1] It is not, however, found in all cases,[2, 6, 25] while other types of cyanotic heart disease may show left axis deviation.[2, 4, 7, 8, 9, 10] The present study was undertaken to analyze the other electrocardiographic findings in tricuspid atresia and to correlate these with the anatomic structure of the heart at autopsy; and also to determine if there were significant differences between these electrocardiograms and those from patients with single ventricle who showed left axis deviation. The autopsy findings on 28 patients with tricuspid atresia and eight with single ventricle were correlated with the clinical and electrocardiographic data. The eight patients with single ventricle included only those who showed left axis deviation in the electrocardiogram: seven of them were cyanotic. Patients with dextrocardia or dextrorotation of the heart were excluded, as were those patients with a single ventricle in whom the electrocardiogram did not show left axis deviation.

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### ANATOMIC DISCUSSION

#### *Tricuspid Atresia*

In this condition, the tricuspid valve is absent and is replaced by a dimple on the lower surface of the right auricle. Blood can leave the right auricle only through a patent foramen ovale or an auricular septal defect. There is but a single auriculoventricular valve, the mitral, which is almost invariably bicuspid, and leads into a hypertrophied left ventricular chamber. The right ventricle, if present, is small and rudimentary and usually communicates with the left ventricle by a septal defect. Rarely, it is a rudimentary blind chamber with no communications. The great vessels may or may not be transposed.

The 28 cases have been analyzed according to the classification of Edwards and Burchell[4] (table 1). This classification assumes that all cases without transposition have pulmonic or subpulmonic stenosis, but one patient (case 21) in the present study, had an increased pulmonary flow and at autopsy the great vessels were seen to be normally placed.

#### *Single Ventricle (Cor Triloculare)*

In this condition, there is a single hypertrophied main ventricle and usually a rudimentary outlet chamber. It differs from tri-

TABLE 1.—*Analysis of Autopsy Findings in 28 Cases of Tricuspid Atresia*

| Case No. | Sex | Age at Death | Vent. Muscle Thickness (cm) | | Size ASD (cm) | Size VSD (cm) | Remarks |
|---|---|---|---|---|---|---|---|
| | | | L. | R. | | | |
| **Group Ia. No Transposition. Pulmonary Atresia** | | | | | | | |
| 1 | F | 7 mo. | 1.0 | | Large | 0 | PDA |
| 2 | F | 16 mo. | | | Large | 0 | PDA |
| **Group Ib. No Transposition. Subpulmonic or Pulmonic Stenosis** | | | | | | | |
| 3 | F | 21 mo. | 1.1 | 0.3 | 1.5 | 0 | Ductus closing bronchials |
| 4 | F | 7 yr. | 1.8 | 0.3 | 2.0 | 0.2 | |
| 5 | F | 8 mo. | 1.0 | 0.5 | 1.5 | 0.2 | |
| 6 | M | 1 yr. | 0.9 | 0.2 | Large | 0.3 | C.S. entered L.A. |
| 7 | F | 10 mo. | 1.0 | | 1.0 | 0.4 | |
| 8 | M | 4 mo. | 0.7 | 0.3 | 2.0 | 0.4 | L.S.V.C. |
| 9 | F | 3 mo. | | | 0.7 | 0.4 | |
| 10 | F | 6 yr. | 1.2 | 0.5 | S.A. | 0.5 | |
| 11 | M | 4 yr. | 1.0 | | S.A. | 0.5 | |
| 12 | M | 19 mo. | 1.3 | | Large | 0.5 | C.S. entered L.A. and R.A. |
| 13 | F | 7 mo. | 0.8 | 0.4 | 1.5 | 0.8 | C.S. Stenosis |
| 14 | M | 3½ yr. | 0.5 | 0.1 | 2.0 | 0.5 | |
| 15 | M | 6½ yr. | 0.8 | 0.1 | 1.3–1.0 | 1.0 | 2 defects in aur. sept. |
| 16 | F | 5 mo. | 0.8 | 0.1 | 3.0 | 0.1 | PDA |
| 17 | M | 21 mo. | 0.7 | 0.2 | 1.0 | 0.5 | PDA |
| 18 | M | 15 mo. | 1.1 | 0.5 | 0.5 | 0.1 | PDA |
| 19 | M | 2 mo. | | | 1.2 | 0.3 | Bronchials |
| 20 | F | 4 mo. | 0.8 | 0.2 | 1.0 | 0.2 | PDA |
| **Group Ic. No Transposition. No Stenosis. Large P.A.** | | | | | | | |
| 21 | M | 18 mo. | 1.1 | 0.3 | 0.8 | 3.0 | 0 |
| **Group IIa. With Transposition and Subpulmonic or Pulmonic Stenosis** | | | | | | | |
| 22 | F | 2 yr. | 1.2 | 0.7 | 2.0 | 2.0 | L.S.V.C. |
| 23 | M | 2½ yr. | | | 0.5 | 0.2 | P.V. entered R.A. |
| 24 | M | 6 yr. | 1.0 | 0.5 | 0.5 | 2.0 | |
| **Group IIb. With Transposition. Without Pulmonic Stenosis** | | | | | | | |
| 25 | F | 5 yr. | 0.9 | | 1.5 | 0.5 | |
| 26 | F | 19 mo. | + | | 0.5 | Large | Aorta overriding |
| 27 | M | 2 mo. | 1.1 | | 3.5 | 0.2 | Coarct. |
| 28 | F | 3 yr. | 1.0 | 0.5 | 1.0 | 2.0 | Narrow L.P.V. |

Abbreviations: C.S., Coronary sinus. S.A. Single auricle. L.S.V.C., Consistent left superior vena cava entering coronary sinus. P.V., Pulmonary vein. ASD, Auricular septal defect or widely patent foramen ovale.

cuspid atresia in the following features: (1) The right auricle communicates directly with the common ventricular chamber. (2) An interauricular communication is not invariably present. (3) Either one or two auriculoventricular valves may be present; if there is but a single valve, it usually has three cusps. (4) Transposition of the great vessels is the rule rather than the exception. (5) In most cases, there is a rudimentary chamber lying in the position of, and possibly representing, the infundibular region or outflow tract rather than a separate ventricle. The vessel arising from the rudimentary chamber is usually stenotic but may be of normal

TABLE 2.—*Analysis of Autopsy Findings in 8 Cases of Single Ventricle Showing Left Axis Deviation in the Electrocardiogram*

| Case No. | Sex | Age at Death | Vent. Muscle Thickness (cm) | A V Valves | Position Rudim. Chamber | Size ASD (cm) | Remarks |
|---|---|---|---|---|---|---|---|
| **Group Ia. With Transposition and Aortic or Subaortic Stenosis** | | | | | | | |
| 29 | F | 8 mo. | 0.7 | 1 | Post. | 3.5 | Hypoplastic aorta |
| 30 | M | 4 days | 0.5 | 2 | Ant. | 1.0 | Coarct. (infantile) |
| **Group Ib. With Transposition and Pulmonic or Subpulmonic Stenosis** | | | | | | | |
| 31 | M | 10 mo. | | 2 | Ant. | None | Pulm. atresia. PDA, overriding aorta |
| **Group Ic. With Transposition and Subaortic and Subpulmonic Stenosis** | | | | | | | |
| 32 | M | 17 yr. | 1.3 | 2 | Post. | None | |
| 33 | M | 14 mo. | 0.7 | 2 | Ant. | None | L.S.V.C. |
| **Group II. Without Transposition, with Pulmonic Stenosis** | | | | | | | |
| 34 | F | 3 mo. | 0.7 | 1 | Post. | 0.2 | L.S.V.C. Pulm. sten. |
| 35 | M | 18 mo. | 0.6 | 2 | Ant. | 2.5 | Tricusp. sten. Pulm. sten. |
| 36 | M | 16 yr. | 1.4 | 2 | Ant. | None | Subpulm. sten. |

caliber. The classification of Rogers and Edwards[11] was adopted.

In the eight specimens examined in this series, the foramen ovale was closed in four cases, patent in three cases, and there was a large auricular septal defect in the other case. Six of the eight cases showed two distinct auriculoventricular valves but in one the tricuspid valve was small and stenotic. An infantile coarctation was present in one instance and in another there was hypoplasia of the aorta (table 2).

### ELECTROCARDIOGRAPHIC FINDINGS AND THEIR INTERPRETATION IN CASES OF TRICUSPID ATRESIA AND SINGLE VENTRICLE WITH LEFT AXIS DEVIATION.

The characteristic electrocardiographic findings in tricuspid atresia are left axis deviation, high peaked P waves, and left ventricular preponderance in the precordial leads[1, 2, 10] (fig. 1).

#### *The P Wave*

The amplitude of the P wave was measured in lead II, where the deflection usually attains its maximum height and shows least variation. The maximum normal amplitude is 2.5 mm. in infants below the age of one year, and 3 mm. in children over that age (10 mm. deflection equivalent to 1 microvolt).[13] Of the patients with tricuspid atresia, 20 had P waves of increased amplitude in lead II, and in the remaining eight the amplitude was normal. In three of these eight cases (cases 4, 8, 22), the P-wave axis, as plotted on the triaxial system of Bayley,[12] was far toward the left (less than 30 degrees) and all of these showed increased amplitude of the P wave in $V_1$ or $V_3$. It was thought that in these patients the normal amplitude in lead II was due to the shift of the P-wave axis. In the remaining five patients with tricuspid atresia the P wave was of normal amplitude in all leads.

The P waves were increased in amplitude in four of the patients with single ventricle (table 3).

#### *Correlation of Electrocardiographic and Pathological Evidence of Right Auricular Hypertrophy*

At autopsy, the right auricle was enlarged in all cases of tricuspid atresia and was hypertrophied in the majority. Since this hypertrophy is theoretically due to difficulty in the expulsion of blood from the right auricle, it should be less marked in the presence of a large associated defect between the auricles. The electrocardiographic evidence of right auricular hypertrophy (high peaked P waves) and the clinical evidence

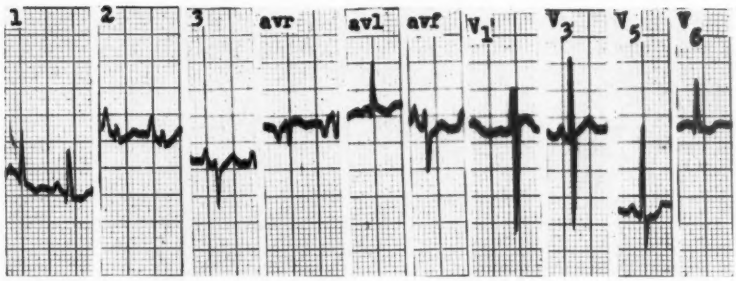


FIG. 1. Typical electrocardiogram in tricuspid atresia, showing left axis deviation, left ventricular hypertrophy, and high peaked P waves (case 9, age 3 months).

(presystolic pulsations at the margin of the liver) were correlated with the size of the interauricular communications found at autopsy. Hepatic pulsations and P waves of increased amplitude were present in 10 of the 28 patients with tricuspid atresia: in all these patients the interauricular communication was small (1 cm. or less in diameter).

There were 13 patients with P waves of increased amplitude who did not show hepatic pulsations: the interauricular communication was small in four of these, measured between 1 and 3 cm. in five, and appeared large but could not be accurately measured in four. The remaining five patients with tricuspid atresia had P waves of normal amplitude in all leads and no hepatic pulsations. In all five the interauricular communication measured over 1 cm. in diameter.

In this series, the combination of high peaked P waves and hepatic pulsations in tricuspid atresia indicated a small interauricular communication. Tall P waves alone, however, were found in some patients with large auricular septal defects.

The P waves were of normal amplitude in four of the patients with single ventricle and increased in amplitude in four. In two of the latter group (cases 33 and 35), hepatic pulsations were present: at autopsy, a marked tricuspid stenosis was found in one, and subpulmonic stenosis with closed foramen ovale in the other.

*The QRS Complex*

The electrical axis was deviated to the left (between plus 30 and minus 90 degrees) in 24 of the 28 patients with tricuspid atresia (fig. 2) and lay between 0 degrees and minus 90 degrees in 23. All the patients with single ventricle included in this study showed left axis deviation. One patient (case 30) had a left bundle branch block, and in another, the electrical axis shifted from minus 80 degrees to plus 110 degrees with each inspiration.

The electrical axis as determined between leads I and II differed from that determined between leads I and III by more than 10 degrees in 9 patients (table 3). This finding indicates that the electrical axis is not always accurately projected on the sides of the Einthoven triangle.

*Unipolar Limb Leads*

Leads $aV_R$, $aV_L$, and $aV_F$ were recorded in 12 cases of tricuspid atresia and four of single ventricle. The heart occupied a horizontal position in 13, and a semihorizontal in two, as indicated by a predominantly positive deflection in $aV_L$ associated with a less positive or negative deflection in $aV_R$. The findings in $aV_R$ are of special interest. The deflection was of the qS type in 9 of the 12 cases of tricuspid atresia, and the R wave present in the remaining three cases measured 1 mm. or less, whereas in two of the four patients with single ventricle, a qR pattern was present and the R wave measured 5 mm. or over. Thus, the presence of an R wave in this lead appears at the present time to be against the diagnosis of tricuspid atresia.

*Precordial Leads*

A predominantly negative QRS deflection in $V_1$ was present in 19 of the 21 patients with tricuspid atresia on whom precordial leads were obtained, and a predominantly positive QRS

TABLE 3.—*Analysis of Electrocardiograph Findings in Tricuspid Atresia and in Single Ventricle Showing Left Axis Deviation*

| Case No. | Age ECG Taken | P Wave | | | QRS, Axis in Degrees | | $aV_R$ | $aV_L$ | $aV_F$ | Time (Sec.) of Onset Intrinsicoid | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Axis in Degrees | Amplitude (mm) | | I-III | (I-II) | | | | | |
| | | | Lead II | $V_1$ | | | | | | $V_1$ | $V_5$ |
| **Tricuspid Atresia** | | | | | | | | | | | |
| 1 | 7 mo. | +75 | 3.5 | | +78 | | | | | | |
| 2 | 15 mo. | +74 | 6.0 | | 0 | (+15) | | | | | |
| 3 | 20 mo. | +30 | 4.0 | | −55 | (−20) | | | | | |
| 4 | 7 yr. | +11 | 2.0 | (3.5) | −13 | | qS | qR | rS | .01 | .04 |
| 5 | 6 mo. | +75 | 3.5 | | −35 | | | | | .02 | .03 |
| 6 | 9 mo. | +37 | 2.0 | | −18 | (+45) | qS | R | RS | .01 | .03 |
| 7 | 4 mo. | +65 | 4.0 | | −35 | | | | | | |
| 8 | 3 mo. | −5 | 0.5 | (3.5) | −30 | (−45) | | | | .02 | .02 |
| 9 | 3 mo. | +72 | 3.5 | | −16 | | rS | qR | rS | .02 | .03 |
| 10 | 18 mo. | +30 | 3.5 | | −14 | | | | | | |
| 11 | 2½ yr. | +73 | 4.0 | | −47 | (+7) | qS | qR | RS | .01 | .03 |
| 12 | 7 mo. | +30 | 2.5 | | +10 | | | | | .01 | .02 |
| 13 | 7 mo. | +45 | 4.0 | | −30 | | qS | qR | rS | .02 | .04 |
| 14 | 3½ yr. | +30 | 1.5 | | −40 | | qS | qR | rS | .02 | .05 |
| 15 | 6½ yr. | +40 | 5.0 | | 0 | (−20) | | | | .01 | .04 |
| 16 | 6 mo. | +90 | 3.5 | | −44 | | | | | .02 | .02 |
| 17 | 18 mo. | +42 | 5.0 | | −60 | | qr | qR | rS | .02 | .02 |
| 18 | 6 mo. | +63 | 7.0 | | −90 | | | | | | |
| 19 | 2 mo. | +49 | 5.0 | | −22 | | qS | qR | RS | .02 | .04 |
| 20 | 3 mo. | +30 | 4.0 | | −20 | | qS | qR | rS | .01 | .035 |
| 21 | 18 mo. | +30 | 5.0 | | −60 | | qrs | qR | rS | .01 | .05 |
| 22 | 2 yr. | 0 | 1.5 | (3.5) | −30 | (−47) | | | | .02 | .05 |
| 23 | 21 mo. | +60 | 3.5 | | −63 | | | | | .02 | .04 |
| 24 | 5½ yr. | +60 | 3.0 | | +70 | | | | | .01 | .04 |
| 25 | 5 yr. | +30 | 2.0 | | −30 | (−13) | | | | .02 | .03 |
| 26 | 7 mo. | +45 | 5.5 | | +55 | | | | | | |
| 27 | 1 mo. | +62 | 2.0 | | −30 | | qS | qR | rS | .02 | .04 |
| 28 | 2 yr. | +50 | 8.0 | | +30 | | qS | RS | R | .02 | .04 |
| **Single Ventricle** | | | | | | | | | | | |
| 29 | 8 mo. | +10 | 1.0 | | −74 | | qR | qRs | rS | .04 | .04 |
| 30 | 4 days | +60 | 2.0 | | L.B.B.B. | | | | | | |
| 31 | 10 mo. | +60 | 2.0 | | −72 | (−51) | | | | .02 | .03 |
| 32 | 17 yr. | +70 | 3.0 | | −80 | | | | | .02 | .03 |
| 33 | 14 mo. | +64 | 6.0 | | −80 | | qr | Rs | rS | .01 | .05 |
| 34 | 3 mo. | +74 | 4.5 | | Varies −80 + 110 | | | | | .02 | .02 |
| 35 | 15 mo. | +37 | 4.5 | | −25 | | qS | qR | rSR | .01 | .05 |
| 36 | 16 yr. | +70 | 3.5 | | −75 | | qR | qR | rS | .02 | .05 |

deflection in $V_5$ in 20. These patterns were considered to indicate left ventricular preponderance. The two patients with an RS pattern in $V_1$ showed a left ventricular preponderant pattern in $V_5$.

Precordial leads were available in seven of the eight cases of single ventricle. A pattern of left ventricular preponderance was present in three, equiphasic QRS deflections in $V_1$, $V_3$, and $V_5$ in three, and right ventricular preponderance in one (figs. 2 and 3).

*The time of onset of the Intrinsicoid Deflection* was measured from the beginning of QRS to the peak of R in $V_1$ and $V_5$. This Q-R interval was

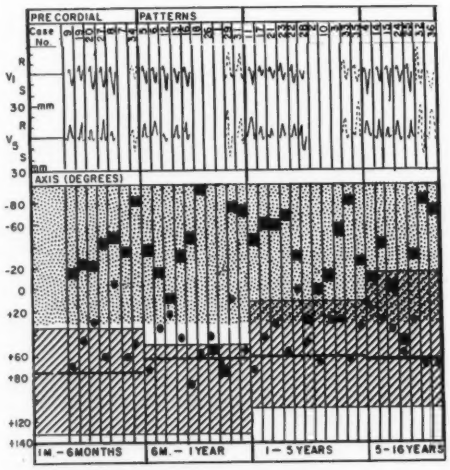


FIG. 2. The electrocardiographic findings in the individual cases of tricuspid atresia and single ventricle. The precordial patterns are shown as a solid black line for tricuspid atresia and as a dotted line for single ventricle. The QRS electrical axis is represented by ■, and is shown in the same column as the axis of the P wave ●, and the precordial pattern for the same patient (case 30 had left bundle branch block and is omitted). Dotted area: Range of left axis deviation (plus 30 degrees to minus 90 degrees). Striped area: Normal range and average QRS axis for age (Ziegler).[13]

normal or below normal in $V_1$ in all patients with tricuspid atresia. In $V_5$, the time of onset was delayed beyond the average normal for the age[13] in 18 of the 21 patients and beyond the upper limit of normal in eight. In case 28, the prolonged Q-R in $V_5$ was the only evidence of left ventricular pathology. In single ventricle, the onset of the intrinsicoid deflection was delayed in $V_1$ in one patient and normal in six: in $V_5$ it was delayed in three of the seven patients (table 3).

*Correlation of Electrocardiographic and Pathological Evidence of Left Ventricular Pathology*

Left ventricular hypertrophy was a constant autopsy finding in tricuspid atresia. In the electrocardiogram of a child, the combination of left axis deviation and a horizontal heart strongly suggests left ventricular hypertrophy. Left axis deviation was present in 24 of the 28 cases and a horizontal electric position was recorded in 9 of the 12 with unipolar limb leads. Additional electrocardiographic evidence of left ventricular hypertrophy was also present: $T_1$ was lower than $T_3$ in 26 instances and the T wave in $aV_L$ was inverted in 10 of 12 records. Isoelectric or inverted T waves in $V_5$ or $V_6$ were found in seven patients. A left ventricular preponderant pattern in the precordial leads was present in 20 of the 21 records.

Although all the patients with single ventricle showed left axis deviation, only three had other electrocardiographic evidence of left ventricular preponderance. In two of these (cases 33 and 35), the unipolar limb leads were similar to those seen in tricuspid atresia: at autopsy, one of these patients had a marked tricuspid stenosis, and in the other the pulmonary artery arose from the posterior main chamber and there was a pulmonary subvalvular stenosis. In both these patients, the part of the ventricular myocardium corresponding to the left ventricle was markedly hypertrophied. In the third patient (case 36), the electrocardiogram differed from

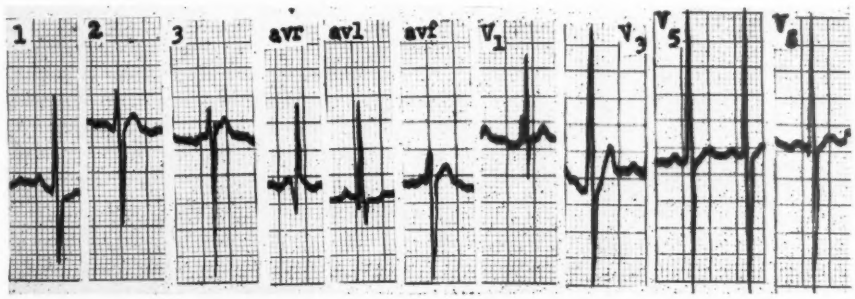


FIG. 3. Electrocardiogram in single ventricle, showing left axis deviation, focal right bundle branch block in $V_1$ and large equiphasic QRS complexes in all precordial leads (case 29).

all the records seen in tricuspid atresia by having a qR pattern in $aV_R$. Autopsy revealed marked subpulmonic stenosis and the pulmonary artery arose from a rudimentary anterior chamber.

*Other Electrocardiographic Findings*

A Q wave was present in one or more of the left ventricular leads ($aV_L$, I, and $V_5$) in 21 patients with tricuspid atresia and three with single ventricle. Such Q waves are believed to originate in the ventricular septum.[19, 20] The presence of these waves in patients with single ventricle, in whom no ventricular septum was present, is of great interest and suggests that the ridge of tissue lying below the rudimentary chamber may contain conduction tissue and represent a rudimentary septum rather than the crista supra ventricularis.

The total electrical systole of the heart, as represented by the Q-Tc,[22] was below the average normal for the age in 20 of the 27 cases of tricuspid atresia: this finding may be associated with a smaller ventricular muscle mass in this condition than in the normal heart.[24] The Q-Tc was normal in the four patients with single ventricle who were not receiving digitalis.

## Summary

The electrocardiographic and autopsy findings in 28 selected cases of tricuspid atresia and eight of single ventricle with left axis deviation were analyzed.

Left axis deviation was present in 24 cases of tricuspid atresia: 20 of the 21 patients with precordial leads showed left ventricular preponderance. Precordial leads were available in seven cases of single ventricle. There were large equiphasic QRS complexes from $V_1$ to $V_5$ in three cases, and right ventricular preponderance in one. The pattern of left ventricular preponderance was seen in three patients; in these no constant anatomical pattern was found at autopsy. In one of the three, the electrocardiographic finding of a tall R wave in $aV_R$ was a point of differentiation from all the records seen in tricuspid atresia. In the other two electrocardiograms, no clinical or electrocardiographic differentiation from tricuspid atresia seemed possible; at autopsy, tricuspid stenosis was found to be present in one of these.

Electrocardiographic evidence of right auricular hypertrophy was present in 23 cases of tricuspid atresia and four of single ventricle. In tricuspid atresia, patients who showed both high peaked P waves and hepatic pulsations were found at autopsy to have small interauricular communications. High peaked P waves in patients without hepatic pulsations occurred in association with auricular defects of varying size. Patients with P waves of normal amplitude in all leads uniformly had large interauricular communications. In single ventricle, right auricular hypertrophy had no uniform correlation with the size of the interauricular communication found at autopsy.

Septal Q waves were found in the left ventricular leads in both groups of patients. It is postulated that the muscle ridge below the rudimentary chamber in single ventricle may represent septal tissue.

The corrected Q-T interval (Q-Tc) was less than the average normal for the age in tricuspid atresia. This suggests that in these patients the excitation wave traverses a smaller bulk of muscle tissue in the normal heart.

## Acknowledgments

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## Summario in Interlingua

Esseva analysate le electrocardiogrammas disponibile in 28 non-seligite autopsiate casos consecutive de atresia tricuspide e in 8 autopsiate casos de univentricularitate seligite de maniera que solo caso exhibiente sinistrorse deviationes del axe esseva includite. Signos electrocardiographic de preponderantia sinistroventricular in le derivationes extremital precordial e unipolar esseva trovate in 27 inter le 28 casos de atresia tricuspide e in 3 del 8 casos de univentricularitate. In solo 2 del casos de univentricularitate esseva le electrocardiogramma identic con illo vidite in atresia tricuspide; in 1 de iste 2 casos stenosis tricuspide esseva presente. Hypertrophia dexteroauricular, indicate per undas P a alte

piccos, insimul con pulsationes hepatic presystolic occurreva in atresia tricuspide in le casos in le quales le autopsia revelava que le communication interauricular esseva parve.

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# Influence of Prostigmine and Acetylcholine on Ventricular Fibrillation Elicited by Focal Cooling

*By* D. Scherf, M.D., R. Bussan, M.D., W. C. Gittinger, M.D. and S. Torin, M.D.

Focal cooling of the exposed ventricle of the dog, beating at high rates, elicits ventricular fibrillation within a few seconds. The effect of this mode of cooling on hearts pre-treated with prostigmine or acetylcholine is studied. These compounds do not prevent ventricular fibrillation, but on the contrary some observations show that they enhance its appearance.

FOCAL cooling of the exposed heart of the dog or cat, which is beating rapidly either regularly or irregularly, is followed within a few seconds by ventricular fibrillation.[6] The higher the ventricular rate of the hearts of these animals is, the earlier ventricular fibrillation appears. By the administration of large doses of atropine this form of fibrillation, initiated by focal hypothermia, was prevented or delayed, provided the cardiac rate was not extremely rapid.[7]

Recently it has been found that prostigmine given during general hypothermia of the dog, particularly if given by means of coronary perfusion, had a decided antifibrillatory effect. When the coronary sinuses of the hypothermic dogs were catheterized, ventricular fibrillation was elicited in 10 of 11 instances. However, ventricular fibrillation failed to occur in 10 experiments when the dogs were pretreated with prostigmine. Acetylcholine had a similar effect.[3, 4] On the other hand, it is known from previous experiments that under the influence of acetylcholine the inclination of the dog's heart to fibrillate following light mechanical stimulation is enhanced.[8, 10] Therefore, we decided to investigate the influence of prostigmine and acetylcholine on the result of focal cooling of the exposed ventricles of the dog.

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This investigation was supported (in part) by a research grant from the National Heart Institute, United States Public Health Service.

Dr. Bussan is a National Heart Institute Trainee.

## Method

The dogs varied in weight from 6.5 to 13.5 Kg. and their hearts were exposed in the manner described in previous reports by the authors.[6, 7] The anesthesia employed was morphine given intramuscularly and Nembutal injected intraperitoneally. The trachea was intubated and controlled respiration was instituted. The dose of prostigmine (Hoffmann-LaRoche) was 1 to 2 ml. of a 1:2000 solution which was injected into the superior vena cava or the right auricle. Similarly, a freshly prepared solution of acetylcholine (Hoffmann-LaRoche) was used in other experiments. In most of the experiments, following the injection of prostigmine, a marked bradycardia resulted so that focal cooling could not be expected to induce ventricular fibrillation according to previous experience. Therefore, in order to increase the rate, aconitine was applied topically to the tip of the right auricle to produce auricular fibrillation. The ensuing ventricular rate was slower than it would have been without the inhibitory effect of prostigmine, but yet faster than during sinus rhythm.

The cooling was accomplished by applying the tip of a small test tube filled with ice to the center of the exposed right ventricle. The electrocardiograms were recorded in lead II.

## Results

*Prostigmine.* Focal cooling after the administration of prostigmine was performed on 13 dogs and ventricular fibrillation appeared in all. As table 1 shows the dose of prostigmine varied between 0.036 and 0.125 mg. per kilogram. In three experiments ventricular fibrillation appeared when the cooling was carried out during sinus rhythm. Once it appeared after a cooling period of only eight and eight-tenths seconds; however, in this instance the heart

TABLE 1.—*Data Obtained in 16 Experiments*

| Date | Weight Kg. | Dose of Nembutal ml. | Dose of Morphine mg. | Prostigmine mg./Kg. | Cooling Period prior to Fibrillation (Sec.) | Heart Rate at Onset of Cooling | Rhythm at Onset of Cooling | Result of Cooling |
|---|---|---|---|---|---|---|---|---|
| | | | | Prostigmine | | | | |
| 5/25/54 | 9 | 3.5 | 160 | 0.055 | 18.2 | 72 | Sinus rhythm | Vent. fib. |
| 6/1/54 | 9 | 4 | 160 | 0.083 | 36.0 | 83 | Sinus rhythm | Vent. fib. |
| 6/8/54 | 13.5 | 6 | 160 | 0.055 | 170.0 | 160 | Aur. fib. | No effect |
| | | | | | 140.0 | 115 | Aur. fib. | Vent. fib. |
| 6/15/54 | 11 | 4 | 160 | 0.091 | 32.0 | 136 | Sinus rhythm | Vent. fib. |
| | | | | | 12.0 | 115 | Sinus rhythm | |
| 6/29/54 | 12.5 | 4 | 160 | 0.040 | 240.0 | 110 | Sinus rhythm | No effect |
| | | | | | 8.8 | 280 | Artif. stim. | Vent. fib. |
| 10/5/54 | 8 | 3 | 160 | 0.125 | 22.4 | 280 | Sinus rhythm | No effect |
| | | | | | | | Artif. stim. | Vent. fib. |
| 10/12/54 | 11 | 3 | 160 | 0.045 | 21.0 | 152 | Aur. fib. | Vent. fib. |
| 10/19/54 | 8.5 | 4 | 160 | 0.118 | 26.8 | 80 | Aur. fib. | Vent. fib. |
| 10/26/54 | 10 | 4 | 160 | 0.050 | 60.0 | 68 | Aur. fib. | Vent. fib. |
| | | | | | 21.0 | 180 | Aur. fib. | Vent. fib. |
| 11/9/54 | 7 | 3 | 200 | 0.071 | 20.8 | | | |
| 11/16/54 | 10 | 3 | 200 | 0.050 | 55.0 | 166 | Aur. fib. | Vent. fib. |
| 11/23/54 | 6.5 | 3 | 160 | 0.077 | 27.0 | 180 | Aur. fib. | Vent. fib. |
| 11/30/54 | 14 | 3 | 180 | 0.036 | 30.0 | 120 | Aur. fib. | Vent. fib. |
| | | | | Acetylcholine | | | | |
| 6/22/54 | 11 | 4 | 160 | 0.182 | 17.4 | 300 | Aur. fib. | Vent. fib. |
| 12/14/54 | 9 | 3 | 200 | 0.022 | 31.0 | 120 | Sinus rhythm | Vent. fib. |
| 12/21/54 | 12 | 4 | 200 | 0.24 | 29.8 | 30 | Aur. fib. | Vent. fib. |

was electrically stimulated at a rate of 280 per minute.

Figure 1 shows the final few seconds of the electrocardiogram before ventricular fibrillation appeared. In the first tracing (experiment of Nov. 23, 1954) auricular fibrillation (induced by the topical application of aconitine) is present and it is seen that this fibrillation

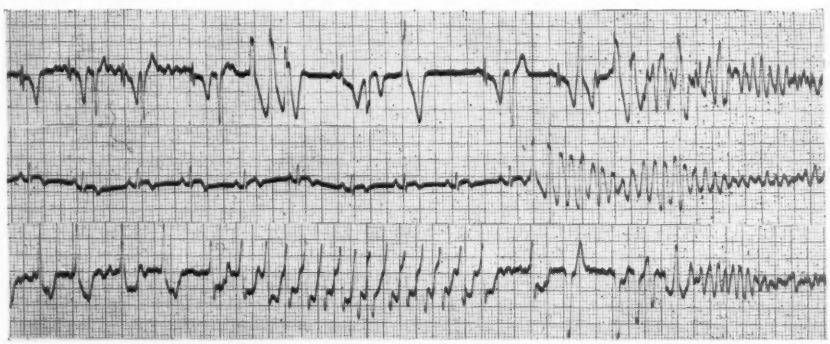

FIG. 1. The three tracings show the terminal phase of topical cooling after the administration of prostigmine and immediately before the appearance of ventricular fibrillation. In figure *1A* auricular fibrillation, caused by the topical application of aconitine to the appendix of the right auricle ends, and right as well as left ventricular extrasystoles appear with increasing rate; in figure *1B* ventricular tachycardia and fibrillation suddenly appear during sinus rhythm; auricular fibrillation existed in figure *1C*; the tracing shows clearly that a series of right ventricular extrasystoles is followed by left ventricular ones and finally by ventricular fibrillation.

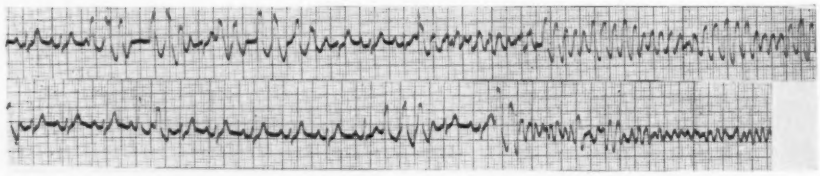

FIG. 2. This experiment (June 15, 1954) shows many right ventricular extrasystoles appearing during cooling after administration of prostigmine in the presence of sinus rhythm. Finally a bizarre electrocardiogram is seen presumably caused by simultaneous appearance of right and left ventricular extrasystoles; ventricular flutter follows and suddenly stops at the end of figure *2A*. Ventricular fibrillation appears on the second attempt at cooling (fig. *2B*).

disappears during the cooling of the right ventricle, a common but unexplained effect.[6, 7] Numerous extrasystoles appear from both the right and left ventricles, suddenly increasing in number and rate, and terminating in ventricular fibrillation.

The second tracing (experiment of June 1, 1954) reveals the sudden onset of ventricular fibrillation during focal cooling performed in the presence of sinus rhythm. In the lowermost tracing (experiment of Nov. 9, 1954) cooling the right ventricle during auricular fibrillation leads to the appearance of a series of right and left ventricular extrasystoles and finally ventricular fibrillation.

Figure 2 shows a phenomenon which was not observed in previous experiments in which focal cooling was done.[6, 7] Cooling for 32 seconds after the administration of prostigmine led to ventricular extrasystoles and finally to ventricular fibrillation and flutter with a rate of 500 beats per minute. This suddenly stopped. Renewed cooling for 12 seconds caused permanent ventricular fibrillation.

Thus, prostigmine does not prevent the appearance of ventricular fibrillation during focal cooling, but some modifications of the usual effects of focal cooling can be seen: 1) Prefibrillatory groups of extrasystoles were common (fig. 1a); 2) fibrillation appeared

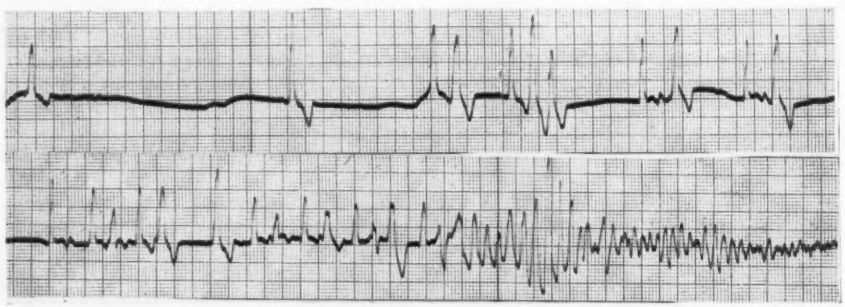

FIG. 3. In this experiment acetylcholine caused auricular fibrillation and marked bradycardia. Cooling elicited extrasystoles with increasing frequency and finally ventricular fibrillation appears.

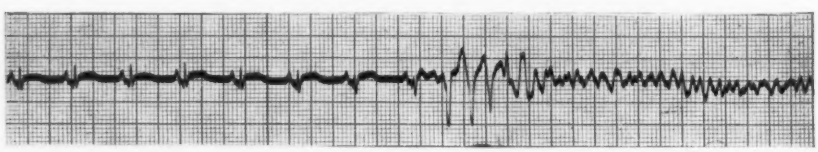

FIG. 4. In this experiment the cooling abolished auricular fibrillation which had appeared after acetylcholine. Suddenly, during sinus rhythm, left ventricular extrasystoles appear, followed by right ventricular ones and by fibrillation.

more readily in the presence of slower rates (fig. 1b); 3) the ventricular flutter encountered disappeared and allowed sinus rhythm to return (fig. 2), a behavior observed very rarely in dogs under any experimental conditions.

*Acetylcholine.* After pretreatment with acetylcholine focal cooling caused ventricular fibrillation within 17.4 to 31 seconds. Here, too, fibrillation appeared in the presence of a relatively slow rate and regular rhythm which is rare in the dog. Figure 3 shows ventricular fibrillation appearing during cooling after administration of acetylcholine in the presence of auricular fibrillation and figure 4 exhibits the same phenomenon occurring during sinus rhythm. The cooling periods, necessary to initiate fibrillation were short.

## Discussion

It must be emphasized that the present experiments do not contradict those obtained with general hypothermia in which it was demonstrated that prostigmine and acetylcholine prevented ventricular fibrillation induced by general cooling. Although topical cooling also leads to ventricular fibrillation, the mechanism need not be the same as that of general cooling. Some effects may be common to both, while there are additional factors peculiar only to focal cooling, i.e., gradients of polarization between the cooled and the noncooled muscle and the fact that lower temperatures are obtained in a circumscribed area of ventricular myocardium than with general hypothermia. The ventricular fibrillation as a result of focal cooling cannot be explained by the release of adrenaline or overloading the heart as it has been postulated in general hypothermia.

In the present experiments topical cooling repeatedly abolished auricular fibrillation as demonstrated in figure 1a. A satisfactory explanation for this phenomenon cannot be given.

The experiments distinctly show the increasing rates of the ectopic ventricular centers before ventricular fibrillation sets in, confirming the studies of Wiggers and his pupils.[2] The experiments with prostigmine as well as those with acetylcholine clearly demonstrate the appearance of extrasystoles of the other, noncooled, ventricle before ventricular fibrillation occurs (fig. 1c, figs. 3 and 4). We are unable to explain these isolated extrasystoles appearing from the noncooled ventricle, but if they occur in conjunction with the extrasystoles originating from the area of the cooled ventricle, we assume that distant centers are awakened by rapid impulses. It is known that rapid electrical stimulation of preganglionic nerve fibers entering a sympathetic ganglion elicits repetitive discharges of the ganglion cells after the initial artificial electrical stimulus has ceased.[1] Similarly, the specific myocardial tissue fibers, if stimulated rapidly beyond a certain critical rate, begin to fire repetitive impulses after the initiating stimulus has been abolished. The importance of this phenomenon for the explanation of ventricular fibrillation is discussed elsewhere.[9]

## Conclusions

Pretreatment of the dog's heart with prostigmine or acetylcholine does not delay or prevent the appearance of ventricular fibrillation initiated by focal cooling of the ventricular surface. The results of the cooling are, however, slightly modified in certain aspects which are discussed.

## Summario in Interlingua

In experimentos con canes le pre-tractamento del corde con prostigmina o acetylcholina non preveniva e non retardava le fibrillation ventricular initiate per frigidation focal del superficie ventricular. Tamen certe aspectos del effectos producite per le frigidation focal esseva levemente modificate per le pre-tractamento mentionate. Iste modificationes es discutite.

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# Electrolyte Changes in Ileal Contents and in Feces during Restriction of Dietary Sodium with and without the Administration of Cation-Exchange Resin

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Sodium and potassium levels of the contents of the terminal ileum and feces were determined for four dogs at different dietary sodium intakes, both before and during administration of a carboxylic cation-exchange resin. With restriction of dietary sodium, there was more sodium bound by the resin in the terminal ileum than was provided by the diet. There was considerable conservation of sodium in the upper gastrointestinal tract, but the colon always absorbed a major part of the sodium presented to it. During resin administration with very low sodium diets there was more sodium in the feces than in the diets.

IN A previous publication[1] we questioned the validity of suggestions, which had been summarized by Bonner,[2] that the failure of cation-exchange resins to hold much sodium in the feces of patients, when they were consuming low-sodium diets, was explainable by the failure of the resins to combine with "endogenous" sodium. We cited evidence that the colon had the function to dynamically absorb sodium and suggested that it might act, in that respect, with sufficient potency to detach sodium from its bonds to the resin. No attempt was made to specify the exchange by which such a detachment of sodium might be effected. Also, McCance[3] had reported decreased sodium concentrations in saliva and gastric juice during sodium depletion resulting from dietary restriction of sodium and diuresis.

We found[1] that the average fecal excretion of sodium of five patients, during 211 patient-days of resin administration and the moderate restriction of dietary sodium to 35 to 52 mEq. per day was 0.48 mEq. per gram of resin. That was contrasted with 2.34 mEq. of sodium that was bound per gram of resin when the resin was in equilibrium, *in vitro*, at a pH of 6.8, with a solution containing the average sodium, potassium and chloride concentrations, reported by Lockwood and Randall[4] to have been found in the dejecta of patients with recent ileostomies.

In a subsequent study,[5] of which we made a preliminary report,[1] we utilized dogs with fistulae into their terminal ileums and found that a severe restriction of dietary sodium to about 1 mEq. per day was followed by a marked decrease in the concentration of sodium in the contents of the terminal ileum. Concomitantly, there was a corresponding increase in the potassium concentration in the ileal contents, which tended to maintain a constant osmolarity. Other than the sodium restriction, the experimental diet was identical with the control diet. That study indicated an effective conservation of sodium in the upper gastrointestinal tract during the dietary restriction of sodium.

The purpose of the present study was to evaluate further the roles of conservation of sodium (active absorption, decreased secretion, or both) in the upper gastrointestinal tract and that of active absorption of sodium by the colon and the relative inefficacy of cation-exchange resins for retaining sodium in the feces of patients whose dietary sodium is much restricted.

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## Methods and Materials

Each dog used in this study was prepared with a valved fistula into its terminal ileum by an adaptation of the procedure of Basso,[6] as previously described.[5] The experimental diets were a previously described bread[5] which was varied only in its sodium content. That was adjusted to the caloric value of the bread so that the first two limitations of sodium intake were proportionate to therapeutic diets containing 1000 and 200 mg., respectively, for an average man. The most severe restriction was proportionate to about 50 mg. per day for an average man. The usual intakes were 1000 to 1200 calories per day. The different breads were fed, once a day, in periods with a descending order of sodium content, usually for four weeks each. During the first two weeks, for each level of sodium content, the bread was fed alone for a control period. After that, during a second two-week period, each day's feeding was followed by the introduction through a stomach tube of 15 Gm. of Resodec, a carboxylic cation-exchange resin 22 per cent in the potassium cycle and 78 per cent in the ammonium cycle. By the method of analysis described below, each packet of Resodec contained the equivalent of approximately 13 Gm. of hydrogen cycle resin. Toward the end of the feeding period of the lowest sodium bread, some of the dogs refused the ration. The bread was then homogenized with water to a thick paste in a Waring blendor and introduced through a gastric tube by a caulking gun. At such times, it was found desirable to reduce the feedings to about 750 calories per day to avoid vomiting.

Samples of ileal contents were aspirated through a 16 F catheter introduced through the fistula. Because of the marked and irregular variations in the electrolyte concentrations in the contents of the terminal ileum,[5] each day's specimen was made by pooling equal amounts of four or five samples collected at hourly intervals, beginning one and one half to two hours after feeding.

Feces were collected for seven-days periods, between carmine markers. Specimens were stored as promptly as possible in a deep-freeze compartment for preservation. All of the specimens in a seven-day period were pooled, thoroughly mixed in a large food mixer and weighed. A tared aliquot of this sample was used in the electrolyte and resin analyses.

For the determination of unbound sodium and potassium, a 10 to 20 Gm. sample of mixed terminal ileal contents or feces was weighed, mixed thoroughly with about 100 ml. of distilled water and centrifuged. The supernatant fluid from this and from three subsequent washings of the solids were decanted into a volumetric flask, made up to volume and analyzed for sodium and potassium with the Barclay internal-standard flame photometer. It had been determined that the resin, saturated with sodium, could stand in distilled water for eight hours without losing an appreciable amount of sodium to the water.

For the determination of the sodium and potassium bound to the resin, the solids were transferred quantitatively from the centrifuge tubes to a beaker, using tenth normal hydrochloric acid as the wash solution. Three normal hydrochloric acid was then added until the pH of the supernatant fluid became 1 or less. It had been found that Resodec quantitatively exchanges any bound sodium or potassium ions for hydrogen ions at a pH below 3. The resultant mixture was then treated, as described above, for the determination of the unbound sodium and potassium.

For the determination of the amount of resin in a sample, a method suggested by the Smith, Kline and French Laboratories, which depends upon the amount of sodium bound when the solids of the specimen are exposed to tenth normal sodium hydroxide, was used. After the solids had stood, with occasional stirring, in such a solution, the mixture was centrifuged and washed three times with distilled water. The solids were then transferred, quantitatively, with exactly 200 ml. of tenth normal hydrochloric acid and the mixture allowed to stand, with occasional stirring for two hours. The mixture was centrifuged and a 50 ml. aliquot of the supernatant fluid was titrated with tenth normal sodium hydroxide, using phenolphthalein as the indicator.

The amount of resin in the sample was then calculated with the following equations, the resin in the hydrogen cycle having been found by analysis, to have a binding-capacity of 10 mEq. per gram.

$$ml.\ 0.1N\ HCl - ml\ 0.1N\ NaOH = mEq\ of\ Na^{+}\ bound\ by\ resin$$

$$\frac{mEq.\ of\ Na^{+}\ bound}{10\ mEq.\ of\ Na^{+}} = Gm\ of\ resin\ (hydrogen\ cycle)\ in\ sample$$

## Results

The data concerning the different levels of approximate sodium intake, the feeding periods, and the pH, the amounts of sodium and potassium, free and bound (by the resin), in both the contents of the terminal ileum and the feces, are presented in table 1. There was a wide range of values in all items. Large hour-to-hour variations in the sodium and potassium concentrations in the terminal ileum had previously been found to occur in samples collected hourly, after each day's feeding; and to be without any consistently reproduced cycle.[5] Consequently, each value tabulated for the ileal contents represents the result of analysis of a pool of equal amounts, obtained by four or five aspirations, at hourly intervals, beginning one

TABLE 1.—*Electrolytes of Contents of Terminal Ileum and Feces in Four Dogs with Fistulae into Their Terminal Ileum, During Progressive Restriction of Dietary Sodium and Resin Administration*

| | | | Ileal Contents | | | | | Fecal Contents | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Free* | | Bound | | | | | |
| Na intake mEq/day | No. dogs | No. weekly periods | pH | $Na^+$ mEq/L | $K^+$ mEq/L | $Na^+$ mEq/Gm. resin | $K^+$ mEq/Gm. resin | $Na^+$ mEq/day | $K^+$ mEq/day | $Na^+$ mEq/Gm. resin | $K^+$ mEq/Gm. resin |
| 73 | 4 | 8 | 5.7 ± .6 (29) | 78 ± 21 (33) | 17 ± 6 (33) | | | 4.6 ± 3.8 (8) | 1.3 ± 1.1 (8) | | |
| 73 plus resin | 4 | 10 | 6.9 ± .3 (38) | 190 ± 41 (38) | 34 ± 11 (38) | 3.7 ± 1.2 (38) | 0.68 ± .18 (38) | 27.9 ± 9.3 (10) | 8.4 ± 2.5 (10) | 2.10 ± .72 (10) | 0.64 ± .19 (10) |
| 17 | 4 | 11 | 5.6 ± .7 (25) | 86 ± 18 (25) | 15 ± 4 (25) | | | 2.9 ± 2.7 (11) | 1.2 ± .6 (11) | | |
| 17 plus resin | 4 | 5 | 6.5 ± .7 (22) | 124 ± 22 (22) | 74 ± 24 (22) | 2.4 ± 1.5 (22) | 1.2 ± .5 (22) | 13.6 ± 6.6 (5) | 16.7 ± 3.6 (5) | 1.05 ± .51 (5) | 1.28 ± .28 (5) |
| 4 | 3 | 6 | 5.5 ± .6 (28) | 34 ± 30 (28) | 58 ± 23 (28) | | | 1.8 ± 1.7 (6) | 2.8 ± 1.6 (6) | | |
| 4 plus resin | 3 | 5 | 6.1 ± .3 (21) | 103 ± 46 (21) | 118 ± 37 (21) | 1.0 ± .8 (21) | 1.1 ± .3 (21) | 5.3 ± 2.5 (5) | 24.2 ± 6.0 (5) | 0.41 ± .19 (5) | 1.86 ± .46 (5) |
| 1 | 3 | 9 | 5.5 ± .5 (27) | 16 ± 8 (31) | 89 ± 15 (31) | | | 0.18 ± .15 (9) | 2.1 ± 1.9 (9) | | |
| 1 plus resin | 3 | 6 | 6.0 ± .4 (23) | 36 ± 24 (23) | 143 ± 32 (23) | 0.24 ± .20 (23) | 1.0 ± .6 (23) | 2.6 ± 1.8 (6) | 20.4 ± 5.5 (6) | 0.20 ± .14 (5) | 1.57 ± .42 (5) |

* Expressed as mEq/L ileal contents.

No. of samples (in parentheses) computed in average, each sample of ileal contents being a pool of equal amounts from 4 or 5 aspirations at hourly intervals: fecal samples were 7-day collectons.

and one half to two hours after a feeding, as described above.

There were no significant changes in the sodium or potassium concentrations in the terminal ileum, during the control periods, without resin, when the dietary sodium was moderately reduced from 6.9 mEq. to 1.8 mEq. for each 100 calories of bread, diets remaining otherwise identical. The latter figure is proportionate to about 1 Gm. of sodium a day, for an average man's caloric intake. However, when the resin was administered after each day's feeding of that moderately low-sodium bread, there was a considerable decrease in both free and bound sodium, and a nearly reciprocal increase in both free and bound potassium in the contents of the terminal ileum, in comparison with the corresponding values obtained during the administration of the resin after each day's feeding of the "normal" sodium bread.

Greater restrictions in dietary sodium, diet remaining otherwise identical, corresponding to 200 mg. and 50 mg. per day, respectively, for an average man, were followed by step-wise decreases in the sodium concentrations and increases in the potassium concentrations in the terminal ileum during the control periods without resin.

When the resin was administered after each day's feeding of the latter two diets, severely and very severely restricted in sodium content, there were further step-wise decreases in both free and bound sodium in the contents of the terminal ileum in comparison with the values obtained during the administration of the resin with the 'normal' and the moderately low-sodium breads. Also, there were further step-wise increases in the concentrations of free potassium, but no significant change in the amount of potassium bound by the resin, with each further reduction of dietary sodium.

## DISCUSSION

Conservation of sodium by the upper gastrointestinal tract was not apparent during the feeding alone of the bread supplying 17 mEq. per day of sodium (equivalent to about 1 Gm. of sodium per day for an average man). It became apparent when the resin was administered during the feeding of that bread. Both the concentration of free sodium and the amount of sodium bound per gram of resin, were then reduced to about two thirds of the corresponding values obtained during the combined feeding of 'normal' bread and resin administration. During the feeding of the breads with lower sodium contents, the con-

servation of sodium by the upper gastrointestinal tract became more prominent, as is shown in table 1.

However, the resin did combine with 'endogenous' sodium. During its administration with each of the breads restricted in their sodium contents, there was more sodium bound by the resin in the terminal ileum than was provided by the diet. The resin administered being equivalent to 13 Gm. of hydrogen cycle resin per day, it may be calculated that, during its administration with the bread with the least sodium restriction, there were more than 30 mEq. of sodium, per day, bound by the resin in the terminal ileum when the diet was providing about 17 mEq. of sodium per day. During the administration of the resin with the diet supplying 4 mEq. of sodium per day, there were 13 mEq. of sodium, per day, bound by the resin in the terminal ileum.

The increase in the potassium concentration in the ileal fluid, which occurred concomitantly with the decrease in its sodium concentration, is of interest. It suggested the existence of a dynamic mechanism for selective absorption, or secretion, or both, of those ions which tends to maintain a constant osmolarity of the ileal contents[5].

The marked increase in the concentrations of free sodium and potassium in the terminal ileum during the administration of the resin over concentrations of the control periods for each level of dietary sodium can not be discussed extensively here. Further studies have indicated that both sodium and potassium were being released from the resin in the terminal ileum faster than they were being absorbed.

The conservation of sodium by the upper gastrointestinal tract is not the sole explanation for the progressively decreased amounts of sodium retained in the feces, as the dietary sodium was progressively decreased. Quantitative evaluation can be only approximated. The volume of the ileal fluid was not measured and its sodium content was determined only during the digestive phase. It was apparent from the moderate density of the ileal fluid that its volume was several (a few) times that of the feces. If it be assumed that the ileal fluids had a volume of 300 ml. per day* with the average sodium contents as charted, then the amounts of sodium recovered in the feces were in the range of 12 per cent to 15 per cent of the sodium contained in the ileal fluids, with the following exceptions. During the feeding of 'normal' bread and resin, 26.0 per cent of the sodium presumed to have been present in the ileal fluid was recovered in the feces. During the feeding of the diet with the greatest restriction of sodium, without resin, only 3.8 per cent of the presumed sodium of the ileal contents was recovered in the feces. When the resin was administered with that diet, 20 per cent of the presumed sodium of the ileal fluid was found in the feces.

Because of the uncontrolled variants, those figures are only approximations. Nevertheless it appears certain that, in the normal dog, during restriction of dietary sodium, its conservation begins to a considerable degree in the upper gastrointestinal tract and increases with the severity of the sodium restriction. Regardless of this, the colon always absorbed a major fraction of the sodium which was presented to it. The colon is an effective sodium-conserving organ.

Despite the potent conservation of sodium in both the upper gastrointestinal tract and colon demonstrated in these dogs, the cation-exchange resin used in these experiments retained sodium in the feces at all levels of restriction of dietary sodium. During the administration of the resin, the absolute amounts of sodium retained in the feces became much less, but the relative amounts of sodium retained became greater as the dietary sodium was more severely restricted. During the feeding of the 'normal' sodium bread and resin, less than half of the dietary sodium was recovered in the feces. During the most severe dietary sodium restriction, with resin administration, more than twice the dietary sodium was recovered in the feces, even though the absolute amount recovered was small. The serum sodium and potassium concentrations in these dogs remained normal during these experiments. In another dog, during a long period of very low sodium diet and resin administration, the

* A value indicated by the usual finding of 1 Gm. of resin in about 20 ml. of ileal contents.

serum sodium became much depressed and symptoms developed.

It is to be considered that these findings were made on presumably normal dogs. They do not explain the marked differences in the retention of sodium in the feces during the long-term administration of this resin to five recently compensated cardiac patients, previously reported.[1] The percentages of sodium excretion found in the feces of those patients were 15.9, 30.8, 35.8, 56.8 and 97.9 per cent, respectively.

## Summary and Conclusions

Four dogs with fistulae into their terminal ileums were fed breads with four different levels of sodium content, but otherwise identical. During periods, with and without the simultaneous administration of a carboxylic cation-exchange resin, for each level of dietary sodium, the free and bound sodium and potassium concentration of the contents of the terminal ileum and of the feces, and the pH of those materials were determined.

During the step-wise restriction of dietary sodium, in the control periods, without resin, there was a step-wise decrease in the sodium concentrations in the contents of the terminal ileum. Concomitantly, there was a corresponding step-wise increase in the potassium concentrations in the terminal ileal contents which tended to maintain a constant isosmolarity.

During the administration of the cation-exchange resin, as the dietary sodium was decreased, there was a step-wise decrease in the free sodium concentrations and a corresponding increase in the free potassium concentrations compared with those of the previous periods of less restricted dietary sodium and resin administration. There was always a greater concentration of sodium and potassium in the ileal fluids during the administration of the resin than when the same diet was fed without resin.

The resin did combine with 'endogenous' sodium. At each level of dietary sodium restriction, there was more sodium bound by the resin in the terminal ileum than was provided by the diet of these dogs.

Although there was considerable conservation of sodium in the upper gastrointestinal tract, the colon always absorbed a major fraction of the sodium presented to it.

The resin retained sodium in the feces of these dogs at all levels of dietary sodium. The absolute amounts of sodium so retained were small during the greatest restriction of dietary sodium, but the fecal excretions of sodium were then twice the sodium intake. Thus, the relative retention of sodium in the feces during the administration of the resin became progressively greater as dietary sodium was decreased.

## Summario in Interlingua

Esseva determinate le nivellos de natrium e kalium in le contento del ileo terminal e in le feces de 4 canes sub varie conditiones de ingestion de natrium, tanto ante como post le administration de un resina carboxylic a excambio de cationes. Quando le ingestion de natrium esseva restringite, le quantitate de natrium ligate per le resina in le ileo terminal excedeva le quantitate de natrium in le dieta. Esseva observate un considerabile conservation de natrium in le tubo digestive superior, sed le colon absorbeva in omne casos un major portion del natrium presentate a illo. Quando resina esseva administrate in conjunction con dietas a bassissime contento de natrium, le feces contineva plus natrium que le dieta.

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# The Relationship of Sodium Retention and Venous Pressures to Edema Formation

*By* RALPH GOLDMAN, M.D. AND SAMUEL H. BASSETT, M.D.

Two patients with congestive cardiac failure were placed on a metabolic balance regimen and supplemental sodium chloride was administered. Weight changes in these patients could be closely correlated with the amount of sodium retention and appeared to be initially independent of brachial venous pressure thus supporting the concept that edema in congestive failure results from primary sodium retention rather than primary elevation in venous pressure.

THE demonstration by Warren and Stead[1] that administration of sodium to patients with compensated heart failure resulted in gain in weight, followed by a rise in venous pressure, was a departure from the concept of edema formation current at the time. It is now generally assumed that factors, other than increased venous pressure may initiate the retention of salt and water. However, it may still be of interest to note that an increase of several kilograms in the amount of extracellular fluid can occur prior to any demonstrable change in the measurement of pressure in the median cubital vein at the elbow. Electrolyte and nitrogen balances, observations of venous pressures, and body weights acquired in the course of a metabolic balance study lent themselves to a quantitative examination of these relationships.

## METHODS

The actual variations in weight of two patients with congestive cardiac failure (patients EHP and EVJ) were related to weight changes arrived at theoretically and calculated from balance data, using the constants proposed by Reifenstein, Albright and Wells.[2] The derived values for the retention of water were then compared with carefully obtained venous pressures.

The metabolic data and the methods employed were obtained by conventional balance technics. Analytic methods were as follows: nitrogen by the Hiller, Plazin and Van Slyke modification of the Kjeldahl procedure directly on the urine and emulsified samples of diet, stool, etc.;[3] chloride by modification of the Volhard silver nitrate—ammonium thiocyanate titration directly on specimens of diluted urine and on solutions of aliquots of diet, feces, emesis and sputum;[4–6] sodium and potassium by the Beckman flame photometer directly on specimens of diluted urine and on solutions of the ash of aliquots of diet, feces, emesis and sputum. Ashing was performed in a muffle furnace at temperatures not exceeding 450 C. Each patient was maintained on two levels of sodium intake, and the effect of adrenocorticotropin was observed at each level. Actual changes in weight were measured on a scale accurate to 10 Gm. Gain or loss in tissue weight was computed as nitrogen balance in grams times 32.[2] This value represents not only the cell increase, but the normally associated extracellular water as well. Total weight change (cell weight plus all fluid change, including both normal and edema fluid) was calculated on the basis of nitrogen balance in grams times 27 (cell weight alone) plus a value for grams of extracellular fluid obtained by dividing the sodium balance by the sodium concentration per milliliter of serum.* The difference between the two calculated values was assumed to constitute edema.

Venous pressures were obtained under basal conditions. The patients were placed supine on a firm bed. At the initiation of the study a horizontal line was painted on the chest wall parallel to, and 10 cm. above, the level of the bed. The patient was rotated until the line was exactly 10 cm. above the bed at each test, and the same arm was always used. This line was the zero level of reference. The skin of the forearm was infiltrated with procaine and a no. 16 needle inserted into the vein. Sodium citrate was used as the anticoagulant. Five minutes were allowed for relaxation of venous spasm, and the fluid column was permitted to rise and to fall to the point of equilibrium as a check of free flow in the system.

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* Correction for the Donnan effect was not applied.

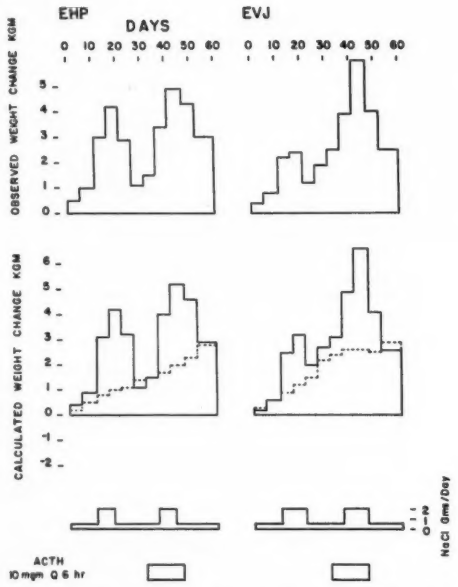


FIG. 1. The relationship of the observed weight changes to weight changes calculated from metabolic balance data. Dotted lines (graph of calculated weight) indicate gains in tissue associated with positive nitrogen balance; solid lines depict the variations in extracellular fluid.

A small carpenter's level was used to relate the zero line on the chest to the column of sodium citrate solution in the manometer.

## RESULTS

Figure 1 shows the result of the calculations based on the metabolic balance data. The upper diagram in each pair indicates the actual changes in weight; the solid line in the lower diagram, the total calculated change, tissue plus edema. The dashed line reveals the portion of the weight curve attributable to tissue gain only. The area between the solid and the dashed lines represents edema (when the solid line is above) or dehydration (when the solid line is below). In both patients the diet was apparently sufficiently high in calories and protein to permit a significant gain of tissue.

The figure illustrates the close parallel between the actual changes in weight of patient EHP (table 1) and the theoretical weights as computed. The cause of the asymmetry of the figure is apparent when it is seen at the end of 60 days the patient had gained 2.5 kg. in tissue as based on calculations made from retention of nitrogen. In patient EVJ (table 2) as in patient EHP, the actual and theoretic weights were closely comparable. An estimate of the amount of edema is plotted in figure 2 and compared with the measurements of the venous pressures. It is evident that both patients could increase fluid retention by 3 kg., present clinical evidence of edema, and yet have no significant change in the brachial venous pressure.

## DISCUSSION

The present study confirms the report of Warren and Stead[1] who demonstrated that edema formation in congestive heart failure precedes the increase in venous pressure and depends upon retention of sodium and water. In our study, the close agreement between the theoretical and the actual fluctuations in weight supports the assumptions made in the calculations. Values based upon nitrogen and sodium balances (as well as nitrogen and chloride) resulted in estimations of weight change which were substantially the same as those observed. It is also apparent from the data that the frequent practice of discounting nitrogen retention in short balance studies is not justified. It can be seen that in 60 days of observation both patients disclosed a tissue gain of over 2 kg. Each had been debilitated by his disease, and it is probable that the weight gain was due to the enforced intake of the test diet which was undoubtedly hypercaloric for the individual.

Earlier studies of the edema in congestive failure, such as those by Schroeder,[7] suggested that, as sodium excretion decreased, water was retained to restore isotonicity. More recent studies have implied that water may be retained primarily, as well as in response to sodium retention. Thus, Schroeder[8] has subsequently found that in one-third of his patients, the chloride loss was less than the proportionate amount of water during recompensation, although chloride and water loss were comparable in the remaining two-

TABLE 1.—*Comparison of Theoretic with Observed Weight Changes*
E. H. P. GH #3617

| Period | No. of Days | 1 N-Bal. Gm. | 2* Cal. Tissue Wt. Change Gm. | 3† Cal. Tissue+ ECW Change Gm. | 4 Sodium Balance Gm. | 5‡ Cal. ECW Change Gm. | 6§ Cal. Tot. Wt. Change Gm. | 7‖ Cal. Edema Gm. | 8 Observed Total Wt. Change Gm. | 9 Observed Total Wt. Kg. |
|---|---|---|---|---|---|---|---|---|---|---|
| I | 5 | 7.89 | 213 | 252 | 0.483 | 154 | 369 | 117 | 490 | 56.33†† |
| | | | | | | | | | | 56.82 |
| II | 6 | 8.78 | 237 | 281 | 0.944 | 300 | 537 | 256 | 490 | 57.31 |
| III | 5 | 8.89 | 240 | 284 | 6.399 | 2030 | 2270 | 1986 | 1980 | 59.29 |
| IV | 5 | 8.59 | 232 | 275 | 3.207 | 1020 | 1252 | 977 | 1200 | 60.49 |
| V | 5 | 1.06 | 29 | 34 | −3.478 | −1110 | −1081 | −1115 | −1260 | 59.23 |
| VI | 5 | 9.59 | 259 | 306 | −7.619 | −2420 | −2161 | −2467 | −1830 | 57.40 |
| VII # | 5 | 4.49 | 121 | 144 | 0.884 | 281 | 402 | 258 | 380 | 57.78 |
| VIII # | 5 | 5.01 | 135 | 160 | 7.105 | 2260 | 2395 | 2235 | 1940 | 59.72 |
| IX** | 6 | 9.81 | 265 | 314 | 3.357 | 1070 | 1335 | 1021 | 1460 | 61.18 |
| X | 5 | 5.61 | 151 | 179 | −2.796 | −890 | −739 | −918 | −660 | 60.52 |
| XI | 8 | 11.43 | 309 | 366 | −5.316 | −1690 | −1381 | −1747 | −1400 | 59.12 |

* Tissue weight change in grams calculated from the constants of Albright, Reifenstein and Wells[3], i.e., nitrogen balance (Gm.) times 27.

† Tissue plus ECW (extracellular water) weight change in grams calculated from constants, i.e., nitrogen balance times 32.

‡ Sodium balance in grams divided by sodium per gram of ECW equals total ECW change in grams (no correction was made for the Donnan effect). Serum sodium concentration averaged 3.18 Gm. per L. with only minor fluctuations.

§ Calculated by adding tissue weight change (column 2) and total ECW change (column 5).

‖ Calculated by subtracting tissue weight change with accompanying ECW (column 3) from total weight change (column 6).

# ACTH, 200 mg., 10 mg. every 6 hours.

** ACTH, 480 mg., 20 mg. every 6 hours.

†† This value represents weight for the beginning of the period, all the others are for the end of the period designated.

thirds. Lombardo[9] noted that on injecting hypotonic sodium chloride there was a relatively greater retention of water than of sodium, and a subsequent fall in the serum sodium. Miller[10] also suggested that water retention preceded sodium retention, since in eight subjects sodium loss during recovery from congestive heart failure was much less than the amount anticipated from fluid and weight loss.

Recently, Squires and his associates[11] found that during recovery from cardiac edema there was a positive potassium balance as well as a loss of water in excess of sodium chloride. This would imply that during the development of cardiac edema there is a dilution of intracellular electrolyte and a loss of cellular potassium. The work of Iseri and associates[12] also revealed a positive potassium balance during loss of cardiac edema. Laragh[13] has observed that the hyponatremia which occurs in certain cardiac patients can be relieved by the ingestion of potassium chloride. It is presumed in this instance that potassium enters the cells and releases sodium to the extracellular fluid. On the other hand, Schwartz and Wallace[14] and Lesser and co-workers[15] noted that, during mercurial diuresis, chloride is the ion that is preferentially excreted (although not in excess of the amount anticipated from the loss of water), while sodium and potassium are both lost in large quantities as the major accompanying cations. Undoubtedly, further work is required to clarify the relationship of potassium exchange to congestive failure, for in our subjects the balances of this element were not significantly affected by mercurial diuretics. The actual decreases in weight compared

TABLE 2.—*Comparison of Theoretic with Observed Weight Changes*
E. V. J. GH #505

| Period | No. of Days | 1 N-Bal. Gm. | 2* Cal. Tissue Wt. Change Gm. | 3† Cal. Tissue + ECW Change Gm. | 4 Sodium Balance Gm. | 5‡ Cal. ECW Change Gm. | 6§ Cal. Tot. Wt. Change Gm. | 7‖ Cal. Edema Gm. | 8 Observed Total Wt. Change Gm. | 9 Observed Total Wt. Kg. |
|---|---|---|---|---|---|---|---|---|---|---|
| I | 5 | 7.93 | 214 | 254 | −0.05 | −15 | 199 | −55 | 840 | 52.17†† |
| | | | | | | | | | | 53.01 |
| II | 6 | 8.73 | 236 | 279 | 0.48 | 157 | 393 | 114 | 160 | 53.17 |
| III | 5 | 10.94 | 296 | 361 | 4.96 | 1615 | 1911 | 1550 | 1370 | 54.52 |
| IV | 5 | 9.52 | 257 | 304 | 1.34 | 437 | 694 | 390 | 40 | 54.56 |
| V | 5 | 10.65 | 288 | 341 | −4.52 | −1470 | −1182 | −152 | −990 | 53.57 |
| VI | | | | | On Pass | | | | | |
| VII # | 5 | 4.73 | 128 | 151 | 0.80 | 262 | 390 | 139 | 550 | 54.04†† |
| | | | | | | | | | | 54.59 |
| VIII # | 5 | 5.30 | 143 | 170 | 5.47 | 1780 | 1923 | 1750 | 1420 | 56.01 |
| IX** | 6 | −0.37 | −10 | −12 | 5.49 | 1790 | 1780 | 1792 | 2100 | 58.11 |
| X | 5 | −4.95 | −134 | −158 | −7.58 | −2470 | −2604 | −2446 | −2030 | 56.08 |
| XI | 8 | 14.11 | 381 | 452 | −5.56 | −1810 | −1429 | −1881 | −1480 | 54.60 |

* See footnote, table 1.
† Serum sodium concentration averaged 3.26 Gm./L. with only minor fluctuations.
‡ § ‖ # See same footnotes, table 1.
** ACTH, 300 mg., 15 mg. every 6 hours.
†† See table 1.

closely with those calculated from the negative sodium balances. This observation is considered important since technical errors in collecting specimens ordinarily result in unexplained deficits in recovery of sodium. However, in view of the variable findings of other authors, it would be fallacious to generalize on the basis of these two patients. No inference can be drawn other than that, in these individuals under the conditions specified, the changes in sodium and extracellular water appeared to be closely and directly related.

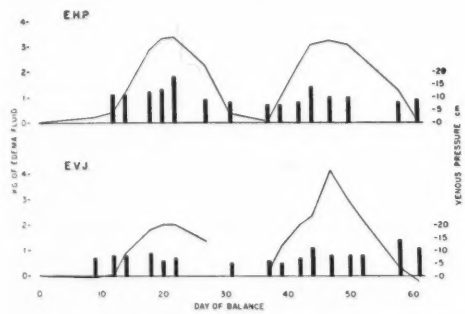


FIG. 2. Relationship of venous pressure (columns) to edema (line graph). Note that accumulation of fluid appears to be independent of a rise in the brachial venous pressure.

## SUMMARY

In carefully-controlled electrolyte balance studies on two patients with congestive heart failure, retention of water induced by sodium supplementation amounted to over 3 kg. and presented as clinical edema.

In neither instance was the edema preceded by an increase in the brachial venous pressure.

The data thus support the concept that retention of fluid in heart failure does not depend upon an initial elevation in venous pressure.

## SUMMARIO IN INTERLINGUA

In cautemente controlate studios del balancias electrolytic in duo patientes con congestive dysfunctionamento cardiac, le retention de aqua inducite per un supplementation de natrium amontava a plus que 3 kg. Illo se presentava sub le forma de edema clinic.

Le edema non esseva precedite per un augmento del pression venose brachial in o le un o le altere del casos.

Le constatationes del studio assi supporta le conception que le retention de fluido in dysfunctionamento cardiac non depende de un elevation initial del pression venose.

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CLINICAL PROGRESS

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# Myocardial Metabolism

*By* R. J. BING, M.D.

## GENERAL METABOLIC CONCEPTS

RECENT developments in our knowledge of the energy producing processes in the cell have stressed the biochemical unity of life: according to this concept, organization does not extend to the lower level of the biologic scale, and biological processes concerned with energy production are quite uniform for different organs and species. In the oxidative processes within the citric acid cycle, the energy released is harnessed to high energy phosphate systems. These oxidative processes are similar in such diversified systems as skeletal and heart muscle, liver, kidney, mammary gland and lens tissue. The intermediary mechanisms of oxidation have been found to be identical in vertebrates, protozoa, molluscs, cockroach muscles, oyster and sea urchin eggs. Thus, the idea is now established that the citric acid cycle is a basic property of living tissues.[1]

In the stepwise processes of cellular oxidation, substrates are utilized with a high degree of efficiency for the performance of vital work instead of being dissipated as heat. It has become likely that adenosine triphosphate (ATP) is the primary energy carrier between the energy-yielding (exergonic) and the energy-requiring (endergonic) functions. Oxidative phosphorylation, resulting in the formation of adenosine triphosphate from orthophosphate and adenosine diphosphate (ADP) is closely associated with the energy producing tricarboxylic acid cycle. Actually, this all-important formation of high energy phosphate primarily occurs as a respiratory chain phosphorlyation which is coupled to the passage of electrons from a reduced carrier to oxygen.[2]

The endergonic synthesis of adenosine triphosphate is localized in elements of the cell, the mitochondria. These structures, called sarcosomes in the heart muscle, are the power plant of the cell, in which the enzymes of the tricarboxylic acid cycle, the respiratory carriers and oxidative phosphorylation are localized.

In contrast to the low degree of specificity found in processes concerned with energy production, energy liberation is highly specific, varying from organ to organ and from species to species. It is here in the manifold processes of energy liberation that evolution has developed the differences of individual organs and species. For example, energy producing mechanisms in heart muscle are quite similar to those in the liver. In the latter, the energy is used in the endergonic and exergonic reaction of intermediate metabolism; the energy in muscle is used as work through contraction.

In its structure, heart muscle does not differ extensively from skeletal muscle. Although it forms a syncytium, electron microscope studies have, aside from the Purkinje fibers, shown no significant changes of cardiac muscle from skeletal muscle. However, the sarcosomes, or mitochondria, are present in greater abundance in heart than in skeletal muscle. It is of great interest that the phosphorylating sarcosomes of cardiac muscle are located contiguous to the A-bands of the myofibrils, indicating the close

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relationship between the site of energy production and the biostructures of energy utlization.[3]

## Fuel for Energy Production in Heart Muscle

Production of energy by the oxidation of carbohydrates, fats, and proteins proceeds in different steps. After conversion of the substrates into amino acids, hexoses, glycerol and water in the intestinal tract, further breakdown to acetyl coenzyme-A α-ketoglutarate or oxalacetate occurs in the individual organ; finally, these products are shunted through the tricarboxylic acid cycle.

The question of relative participation of carbohydrates, fats or proteins in the energy production of the heart muscle can be investigated by use of metabolic studies on tissue slices or tissue homogenates, on the isolated heart in vitro and on the intact heart in situ. Each of these methods possesses certain advantages and disadvantages. For example, with the use of tissue slices or tissue homogenates, the stepwise fate of foodstuffs through the metabolic pathways can be followed, particularly if radioisotopes are being used. However, the use of these artificial models does not reveal the properties of the system as a whole, and certainly the conditions under which the studies are made are highly artificial. By studying the whole heart outside the body, in systems such as the heart-lung or the heart-oxygenator preparation, observations are, by necessity, restricted to acute processes and changes only; here, too, the separation of the individual organ from its internal environment is likely to result in artificial conditions which are not conducive to normal physiological function. Metabolic studies carried out on the intact human or animal heart in situ have the disadvantage that only overall, and not intermediary, changes can be observed. The concentration of the substrate entering or leaving the organ is known, but the fate of this substrate within the cell is unknown. This is because the catalytic systems cannot be individually explored and their chemical properties cannot be established. But these studies have the advantage that they are carried out under physiological conditions in a natural and relatively undisturbed environment.

## Carbohydrate Metabolism of the Heart

By using tissue slices or the isolated heart of dogs, it has been found that glucose, pyruvate, and lactate can be utilized by the heart. As in the intact heart in situ, the rate and utilization of pyruvate and lactate by cardiac muscle appear to be a function of the initial concentration of the substrate.[4] As is to be expected, oxidation of pyruvate to carbon dioxide and water in the Krebs cycle takes place in the mitochondrial system of the heart. Work on the heart-lung preparation has suggested the possibility that lactate is the most important fuel substance of the heart.[5] It was even thought that lactate could be utilized by the heart for direct combustion while sugar was primarily utilized for the formation of glycogen.[5] The results obtained on carbohydrate usage of the isolated heart may be summarized as follows: (1) the myocardial uptake of glucose and lactate appears to be a function of the arterial concentration and the addition of lactate lowers myocardial glucose usage; (2) even if carbohydrates are considered as completely oxidized, there is still a margin of 70 per cent of the myocardial oxygen usage not accounted for, suggesting that carbohydrates are not the sole fuel of the heart and (3) the work of the heart and its oxygen supply appear to play an important role in determining the usage of carbohydrates.

Some of these observations could be confirmed on the whole heart, using the technic of coronary sinus intubation. In this procedure, a catheter is introduced through an arm vein and the right atrium into the coronary sinus.[6] The test can be carried out on unanesthetized dog and man. It permits sampling of coronary venous blood; thus the arteriovenous difference (the extraction) of carbohydrates, fats, proteins, amino acids, and oxygen by the heart can be determined. Since the coronary blood flow can be measured with the nitrous oxide method, the myocardial usage (coronary blood flow times the coronary arteriovenous extraction) of various substrates and oxygen can be

calculated.[7] Calculations of the contribution of each individual metabolite to the aerobic metabolism of the heart muscle (the oxygen extraction ratio) are also possible. The oxygen extraction ratio represents the ratio of the oxygen equivalent of the substrate extracted to the total myocardial oxygen extraction (oxygen equivalent of substrate extracted by the myocardium/myocardial oxygen extraction). Although the principle of this calculation is sound, there is little doubt that the oxygen extraction ratios represent only approximations. This is because in heart muscle, as elsewhere in the organism, which is in dynamic equilibrium, both storage and conversion of foodstuffs take place; thus the oxygen consumed or extracted by the heart is not necessarily used for energy production alone, but for storage or conversion as well. Under these conditions, the exact contribution of oxygen consumed to energy production cannot be ascertained. For example, the oxygen extraction ratio of fatty acids rises above 100 per cent after ingestion of a diet containing a large quantity of fatty acids. This is quite impossible on the basis of oxidation alone, and can best be explained on the basis of storage of fatty acids in heart muscle.[7]

Using the technic of catheterization of the coronary sinus in unanesthetized patients without heart failure, it has become apparent that both myocardial glucose usage and extraction are functions of the arterial glucose concentration.[8, 9] At low arterial glucose concentrations (below 80 per cent) the coronary arteriovenous glucose difference is less than 4 mg per 100 cc. As the arterial glucose concentration increases, the myocardial extraction of glucose rises rapidly until at blood concentrations of above 110 mg. per 100 cc. the extraction of glucose appears to have reached its maximal value. This relationship between arterial glucose concentrations and myocardial uptake of glucose is very similar to that obtained in the eviscerated dog.[10] The S-shape of the curve indicates that at low blood sugar levels, substances other than glucose are utilized and that there is a maximal capacity for the utilization of glucose. Between these upper and lower limits, utilization of glucose varies directly with the height of the blood sugar.

TABLE 1.—*Relative Contribution of Carbohydrates and Non-Carbohydrates to Total Myocardial $O_2$ Usage*

| Carbohydrate % | | Non-carbohydrate % | |
|---|---|---|---|
| Glucose | 17.90 | Fatty acids | 67.0 |
| Pyruvate | 0.54 | Amino acids | 5.6 |
| Lactate | 16.46 | Ketones | 4.3 |
| Total | 34.90% | | 76.9% |

As in the case of glucose, myocardial utilization of lactate is dependent upon its arterial concentration.[8] At normal blood concentrations glucose and lactate are used by the human heart in approximately equal amounts. (table 1)

Similar to the perfused dog's heart, the human heart appears to utilize pyruvate.[8] Although the blood concentrations and the myocardial extractions of this metabolite are small, it plays an important role in intermediary metabolism. Therefore, although pyruvate carried to the heart in coronary arterial blood is of little importance in contributing to the energy production of the heart, the pyruvate balance of the heart is a sensitive indicator for disturbances in myocardial metabolism induced by myocardial ischemia or anoxia.

Similar to the human heart, the dog's heart utilizes carbohydrates according to the concentration in arterial blood, and there is no reciprocal relationship between arterial con-

TABLE 2.—*Disturbances in Myocardial Metabolism*

I. Disturbances in energy production with reduced cardiac efficiency.
  A. Beri Beri heart disease.
  B. Myocardial ischemia and anoxia.
    1. Hemorrhagic shock.
    2. Coronary occlusion.
    3. Ventricular fibrillation.
    4. Hypothermia.
II. Disturbances in energy production without decreased cardiac efficiency.
  A. Diabetes.
III. Disturbances in energy utilization with reduced cardiac efficiency.
  A. Congestive failure.

centration and myocardial extraction of one metabolite to the other. The work of the heart or the coronary blood flow have no influence on the myocardial extraction coefficient of glucose, pyruvate, or lactate.[11]

The main conclusions to be drawn from these studies on carbohydrate metabolism on the human and dog heart are, therefore; that the arterial concentrations of carbohydrates determine their myocardial usage, cardiac work does not influence their utilization, and the total aerobic metabolism of glucose, lactate, and pyruvate combined falls short of the total oxygen consumption of the heart (table 2).

### Metabolism of Ketones, Amino Acids and Fatty Acids

Results obtained from tissue slices, tissue homogenates, and the isolated heart in vitro have already suggested that heart muscle uses noncarbohydrate substances. Green and associates, for example, found that soluble preparations from heart muscle catalyzed the oxidation of fatty acids.[12] Similar results were obtained by Ochoa.[13] Heart mitochondria can convert acetate to its active form, providing oxidation of any member of the citric acid cycle is taking place concurrently.

The respiratory quotient of the isolated heart diminishes or is low in animals when they are fed on a diet consisting largely of butter. As much as 80 per cent of the total metabolism of isolated heart may be derived from sources other than carbohydrates.[14] Furthermore, the respiratory quotient of the perfused isolated heart is seldom unity, again suggesting utilization of fats. From analysis of fatty acids in heart muscle and blood perfusates, it was concluded that cardiac fat was replenished from blood fatty acids and the source of cardiac energy, insofar as it is derived from fats, is the blood fatty acid.[15]

The utilization of ketone bodies by the isolated heart has been demonstrated by a series of investigators.[7] Thus $\beta$-hydroxybutyric acid can be utilized by the isolated heart. There was no evidence of any definite relationship between utilization of carbohydrates and acetone bodies, indicating that oxidation of ketones was not dependent upon carbohydrate oxidation. Thus, there is general agreement as to the usage of fats and ketones by the isolated heart.[7] In contrast, it was concluded that neither naturally occurring amino acids nor those not occurring in nature are utilized by the isolated heart.[7, 9] It seems quite possible, however, that the failure of these investigators to detect ammonia resulted from the fact that it did not remain free in blood, most of it having been taken up by glutamic acid to form glutamine.[7]

Studies on the human and dog heart using catheterization of the coronary sinus have confirmed some of the data collected from in vitro experiments. Thus it was found that the human and the dog heart can utilize considerable quantities of fatty acids, ketone bodies, and amino acids[7] (table 1). Definitive proof of the usage of fatty acids by the human heart has been obtained in tests in which the fatty acid levels in blood were increased by high fat intake. In these patients, the myocardial extraction ratio of fatty acids was frequently above 100 per cent, and statistical analysis confirmed the difference between patients in the postabsorptive state and after ingestion of fatty acids.[7] Two possible explanations for the high fatty acid uptake by the myocardium can be suggested: that the metabolism of fatty acids was increased and that storage of fat in the heart muscle had occurred. It has long been known that skeletal muscle utilizes fat, and it is likely that the ratio of fats to proteins used by the muscle depends upon the relative amount of the two foodstuffs available, and the ability of the enzyme systems to oxidize carbohydrates. Thus in the starving subject, in which the glycogen reserve in the liver has been exhausted, skeletal muscle derives most of its fuel from the metabolism of fat. It is likely that even with a slight fall in circulating carbohydrates, most of the energy production of the heart is sustained by fats. Thus it has been shown that after an overnight fast, three-fifths of the energy production is sustained by fat.[16] Apparently where there is no continuous exogenous supply of carbohydrates, endogenous supply is used with increasing

economy.[16] Evidence for storage of fat in heart muscle had already been obtained by Wegelin, who produced alimentary lipemia and demonstrated fatty infiltration into the intrafibrillar sarcoplasm and the cross-sectional parallel fibers of heart muscle.[17]

Ketones are also utilized by the human and dog heart, the aerobic metabolism of ketones accounting for approximately 5 per cent of the total oxygen extraction[7] (table 1). The contribution of ketones to the oxidative metabolism of the heart is much greater in the diabetic patient and in alloxan diabetic dog. It is likely that ketone utilization by the heart is governed by their arterial concentration and by the quantity of carbohydrate available.[7] The metabolic pathway of ketones in heart muscle is not clear from these studies. It is possible, however, that under certain conditions, such as diabetes or starvation, ketones take over some of the energy producing functions in the muscle.[16] Apparently carbohydrates inhibit ketone utilization by the heart, a finding which is in accord with Krebs' demonstration of competitive inhibition (e.g., deamination of amino acids is inhibited by oxidizable substrates.[18] A similar competition was found in the liver between fatty acids and other oxidizable substrates.

In contrast to the heart-lung preparation, the human and dog heart in situ extracts considerable quantities of amino acids from the coronary blood.[7] After infusion of amino acids, as much as 40 per cent of the total cardiac oxygen consumption can be accounted for by aerobic metabolism of amino acids. A small rise in arterial amino acid concentration of 20 per cent produces a disproportionate increase in the myocardial extraction of 245 per cent. The high uptake of amino acids by the heart does not indicate storage, as in the case of fatty acids or glycogen. Oxidation of amino acids probably leads eventually to the formation of some member of the citric acid cycle, which in turn is burned to completion, furnishing high-energy phosphate to be utilized for muscular contraction. Another possibility is that some of these amino acids can form glycogen, which can be stored in the heart to be used later for the production of energy. Finally, amino acids may be transformed into other nitrogenous compounds and find their way not only into other amino acids, but into the whole protein structure. It is likely that in the heart, as in other organs, there is a continuous exchange between exogenous and endogenous amino acids, both of which can be taken up by tissue proteins. Enzymes exist in the mitochondria which catalyze the transamination of certain amino acids.[2]

Tests performed on the human and dog heart in vivo, therefore, have demonstrated that heart muscle can utilize glucose, lactate, pyruvate, fatty acids, ketone bodies, and amino acids. This great versatility of the myocardium may be regarded as an important factor of safety.[9] If the heart were dependent upon carbohydrates alone for its food supply, only a fraction of its energy requirements could be covered, even with adequate arterial glucose concentrations. It appears that the main factor of determining the extraction of any individual metabolite from the coronary blood is its arterial concentration; however, it is likely that the relationship between utilization of carbohydrate and noncarbohydrate material is influenced by their relative availability and by the ability of the enzyme systems of the heart to catalyze carbohydrates.

## Disturbances in Myocardial Metabolism

The technic of catheterization of the coronary sinus has been of particular value in investigating disturbances in myocardial metabolism. Metabolism may be defined as the sum of chemical changes in the living cell by which energy is provided for vital processes. This encompasses processes of energy production. However, the present discussion will include disturbances of energy liberation as well. Abnormal myocardial extraction of foodstuffs suggests that the disturbance is within mechanisms concerned with energy production. Of course it is possible that the changes within intermediary metabolism are so subtle that they do not become apparent with the methods which rely on determinations of substrates in coronary arterial and venous blood. To use a comparison, a man observing the door through which the actors leave the

stage on which a play is being performed cannot reconstruct the play with certainty by watching the actors enter and leave. The observer can, however, reconstruct for himself some of the plot by closely observing the appearances, the costumes and the attitudes of the actors.

All in all, the evidence for the localization and nature of the metabolic defect within processes of energy production as gathered from determinations of coronary arteriovenous differences is quite indirect. The same may be said with reference to localization of disturbances within energy liberation. In the heart, energy is liberated in the heart muscle, more specifically in the contractile proteins. Only by exclusion can one ascribe disturbances in cardiac function to interference with energy liberation. Only if the myocardial extraction and usage of substrates appears normal in the presence of diminished cardiac efficiency or reserve can one assume that energy liberation is at fault. But here again it is difficult to localize the defect. Heart muscle is a complex structure, composed of a series of contractile proteins, which are subject to a combination of enzymes and electrolytes; the search for the exact location of the deficiency is complicated and involved, and cannot be carried out on the intact heart.

Table 2 illustrates that disturbances in cardiac metabolism have been divided into those of energy production and those of energy liberation and utilization. Subdivisions were made depending on whether the mechanical efficiency of the heart is altered. The mechanical efficiency of the heart represents the percentage ratio of the work of the heart to its energy cost (oxygen usage) expressed in energy units. The efficiency of the normal left ventricle of man is approximately 25 per cent, or 25 per cent of the chemical energy (the myocardial oxygen usage) is converted into useful work of contraction. Consequently, a fall in efficiency could result from a decline in cardiac work or an increase in cardiac oxygen usage. In most clinical conditions, myocardial efficiency declines because of a fall in cardiac work and not because of an increase in the myocardial oxygen consumption.

*I. Disturbances in Energy Production Resulting in Diminished Cardiac Performance and Efficiency*

Deficiency in energy production can occur at any level within the hierarchy of enzymes catalyzing processes concerned with energy production. Because of the close interrelationship of these enzymes, disturbances of one phase of metabolism may also produce alterations in other metabolic pathways. On the other hand, the disturbance may remain localized, as appears to be the case in myocardial ischemia accompanying hemorrhagic shock. Why some of the metabolic disturbances result in diminution of cardiac efficiency, eventually leading to myocardial failure, while others do not, is difficult to answer. It is possible that the localization of the metabolic defect is of importance. For example, interference with cocarboxylase mechanisms, as observed in hemorrhagic shock and coronary occlusion, blocks the pathways of the carbohydrate substrate into the citric acid cycle; this may lead also to interference with fatty acid catabolism. Thus, energy production is seriously curtailed. In contrast, in diabetes mellitus, myocardial reserve and efficiency are not diminished because although the diabetic heart is deficient in carbohydrate, fat and protein metabolism, mechanisms concerned with energy production are probably not as seriously interfered with and enough metabolic detours are available to safeguard operation of the metabolic furnace.

*A. Beri-beri Heart Disease.* In this nutritional deficiency, tissue cocarboxylase is depleted because of a deficiency of dietary thiamin. As a result, pyruvate is not broken down into acetyl coenzyme-A, and completion of carbohydrate metabolism through the citric acid cycle is interfered with. Blood concentrations of pyruvate and lactate increase. It is difficult to say whether myocardial failure ensues as a result of interference with energy production or because of increased cardiac work resulting from the possible vasodilator effect of pyruvate. An abnormal pattern of myocardial metabolism has also been demonstrated in dogs during acute and chronic thiamin deficiency. The myocardial utilization of pyru-

vate was normal despite elevated arterial pyruvate concentrations. Myocardial extraction of lactate was also inhibited, possibly due to the adverse effects of elevated pyruvate levels on lactate dehydrogenase.[19]

*B. Myocardial Ischemia and Anoxia.* Table 2 illustrates that myocardial ischemia can be considered as a separate metabolic entity, because in conditions belonging to this group, both the stimulus for the metabolic alterations and the metabolic response of the heart muscle are similar, varying only in degree with the severity of ischemia.[9] In hemorrhagic shock, the degree of ischemia is relatively minor, and therefore the metabolic changes are few. In coronary occlusion and particularly in ventricular fibrillation the myocardial ischemia is extensive and the metabolic changes are pronounced. Hypothermia is included in this category because here, too, the coronary flow is reduced. However, the extraction of various substrates by the heart is usually normal. This suggests that the metabolic response of the myocardium to reduced coronary flow is influenced by the ratio of oxygen demand of heart muscle to its oxygen supply. If oxygen demand and supply are proportionately diminished, the metabolic effects of myocardial ischemia are slight or absent. This is the case in hypothermia and probably also in hypothyroidism.

1. *Hemorrhagic Shock:* Observations in the literature have suggested the possibility that the deterioration of myocardial expulsive power observed in hemorrhagic shock contributes to circulatory failure; this myocardial depression was thought to be responsible for the re-appearance of circulatory failure during the phase of hemorrhagic shock in which the blood loss incurred in the oligemic phase had been replaced (the normovolemic phase).[20] Available evidence suggests that metabolic changes within the heart muscle, triggered by reduced myocardial oxygen usage are responsible for the myocardial depression. There is little doubt that the coronary flow, and therefore the myocardial oxygen usage, are reduced during both oligemic and normovolemic phases of shock.[21] Myocardial efficiency is reduced because the cardiac work decreases proportionately more than the myocardial oxygen consumption. Diminished cardiac performance (reduction in cardiac output) leads to stagnant anoxemia during oligemia with resulting increase in peripheral extraction of oxygen and an elevation in the concentration of glucose, lactate and pyruvate. During normovolemia, arterial concentration of pyruvate remains elevated.[20]

These changes occurring in the blood as a result of tissue anoxia have been known for a great length of time. The question arose, however, whether the enzyme systems of heart muscle are affected to a similar degree. The most significant change in myocardial metabolism is a diminution in pyruvate usage, with an actual increase in that of lactate. In most instances the pyruvate level in coronary vein blood exceeds that of arterial blood in both oligemic and normovolemic phases of shock.[21] Furthermore, despite increased arterial glucose concentration during oligemia, myocardial extraction and usage of glucose are reduced.[21] Most of these changes persist after retransfusion of blood. Apparently the infusion of blood is unable to correct the metabolic disturbance initiated during the oligemic phase. It is likely that in hemorrhagic shock the myocardial ischemia is not severe enough to result in lactate production by the heart via the usual glycolytic scheme. The fact that negative myocardial pyruvate balance occurs during both oligemic and normovolemic phases suggests that there is interference with cocarboxylase activity. This coenzyme is destroyed under anaerobic conditions and its disappearance is thought to result from its dephosphorylation.[22, 23] Therefore, in hemorrhagic shock the myocardial block is identical with that encountered in beri-beri heart disease. However, in the former, cocarboxylase is destroyed because of anoxia, whereas in beriberi heart disease its formation is diminished because of absence of adequate dietary thiamin.

2. *Experimental Coronary Occlusion and Coronary Shock:* It is recognized that myocardial infarction in man is frequently followed by a fall in blood pressure. In the analyses of Mintz and Katz, 74 per cent of their patients exhibited a fall in systolic blood pressure of

between 10 and 79 mm. Hg, the largest drop being 180 mm. Hg.[24] It is likely that the pathogenesis of shock in acute myocardial infarction is the combined result of diminished cardiac output and increased vascular resistance. It might be expected that in patients with severe fall in blood pressure, the coronary flow is further reduced because of diminished pressure head in the aorta. On the basis of data obtained in experimental hemorrhagic shock, it is likely that this leads to metabolic changes in the myocardium. Such changes occur in experimental coronary occlusion in the dog produced according to the method of Agress.[25]

In this procedure plastic microspheres of 325 mμ. diameter suspended in gum acacia are injected into the coronary arteries of the dog by means of a special catheter. Agress and associates produced an average fall in blood pressure of about 30 per cent. In our experiments the quantity of spheres injected was greater and therefore the fall in blood pressure more pronounced (60 mm. Hg or about 50 per cent of the initial pressure.) There was an immediate statistically significant fall in cardiac output, coronary blood flow and myocardial oxygen consumption. Out of a total of 17 experiments, myocardial extractions of glucose became negative in 5, those of pyruvate in 11, and those of lactate in 9 experiments. In many instances, both potassium and inorganic phosphate appeared in increased amounts in coronary vein blood. Apparently, the myocardial ischemia had led to serious interference with the normal extraction of these substrates and electrolytes. In most animals these changes were fleeting, appearing only for the period immediately following the creation of the infarct. In a few animals the disturbed metabolic function persisted for the duration of the experiment (30 minutes).[26]

Apparently in myocardial infarction the disturbance in pyruvate metabolism is similar to that encountered in hemorrhagic shock. However, artificial coronary occlusion appears to result in more severe metabolic changes, as demonstrated by the finding that both glucose and lactate appear in increased concentrations in coronary vein blood.

3. *Ventricular Fibrillation:* Since the severity of metabolic changes in heart muscle appears to depend on the degree of myocardial ischemia, the changes should be particularly pronounced in ventricular fibrillation in which the coronary flow is almost nonexistant. In eight dogs, in which ventricular fibrillation was produced by electric shock, both pyruvate and lactate concentrations in coronary vein blood rose exceeding those in arterial blood in every experiment.[26] The coronary arteriovenous difference of glucose and ketones also diminished and in six animals the glucose and ketone concentrations in coronary vein blood exceeded those in arterial blood. Potassium also appeared in increased concentration in coronary sinus blood. In all likelihood, coenzymes and adenosinetriphosphate are maintained in their phosphorylated form only as long as active oxidation is assured. Once oxidation is arrested, the coenzymes break down and the process becomes irreversible, unless oxidation takes place before this has occurred.

4. *Hypothermia:* The statement has been made in a previous paragraph that the severity of metabolic disturbances in heart muscle depends on the ratio of oxygen demand to oxygen supply. If the oxygen demands of the heart and its oxygen supply can be diminished in the same proportion, the metabolic disturbance of anoxia on the heart is likely to be moderate.

It has been generally known that reduction of body temperature to 22 degrees can be tolerated, but there has been some controversy as to the role played by the heart in the causation of death during hypothermia. It was felt by some that death was due to cardiac hypoxia, while others believed that oxygen utilization of the heart remains normal since no changes in coronary arteriovenous oxygen difference were found with hypothermia. The frequency of ventricular fibrillation at low body temperature has been known for many years.

Data obtained in dogs using intubation of the coronary sinus illustrate that as the body temperature of dogs falls to 26 C. the coronary flow, the myocardial oxygen usage and the left ventricular work and efficiency decline.[27] In contrast, coronary arterio-venous oxygen extraction does not change. Although the

decline in left ventricular oxygen consumption is considerable, the fall in oxygen usage of the whole animal is proportionately greater. As a result, the ratio of oxygen consumption of heart to the total oxygen consumption increases during hypothermia; this indicates that the heart maintains a relatively high oxygen consumption as compared to the rest of the body.[27]

Although in a few animals with decreased arterial oxygen saturation hypothermia may result in negative myocardial glucose balance, in general the myocardial extraction and utilization of glucose, lactate and pyruvate are not altered.

*II. Disturbances in Energy Production Without Decrease in Cardiac Efficiency*

*Diabetes.* In contrast to the disturbances discussed in the previous category in which the metabolic derangements in the heart muscle have led to a diminution in the mechanical efficiency and cardiac reserve, the cardiac performance in diabetes not accompanied by coronary sclerosis is normal. Studies on metabolism in diabetes have in the past been mainly concerned with metabolic changes of the whole organ, or the liver in particular.[28, 29, 30] Generally, it has been assumed that more than one metabolic disturbance is present in diabetes. Difficulties in transfer of sugar across the cell membrane, interference with the hexokinase reaction, defects in oxidative phosphorylation connected with the generation of high energy phosphate, and disturbance in synthesis of fatty acids have all been implicated.[28] Unquestionably, in this disease, the oxidation of glucose is decreased. It is likely, however, that this decrease is only relative, because, although the utilization of glucose is less than in normal animals with similar hypoglycemic levels, it is still above that of the normal animal at its usual blood sugar level.[31]

Few studies have been carried out on the diabetic heart in situ. Glucose seems to be utilized by the diabetic heart in the heart-lung preparation. However, it is likely that the utilization of glucose by the heart is diminished.[32, 33] This also applies to pyruvate and lactate, since it has been found that cardiac tissue slices from diabetic dogs utilize those metabolites less readily than those of normal animals.[34] Diminished utilization of $C^{14}$-labelled pyruvate has also been observed in both cardiac and diaphragmatic muscle of diabetic animals and the proportion of pyruvate converted to carbon dioxide is decreased.[35] Using pyruvate labelled with $C^{14}$ Hastings found that the addition of insulin in vitro increased the conversion of labelled pyruvate to $C^{14}$-carbon dioxide in the diaphragm of the diabetic animal, but not in cardiac muscle.[35] Apparently, the diabetic heart in the heart-lung preparation shows no deficiency in lactate utilization and derives most of its energy from proteins and fatty acids.[33]

The disturbances in fatty acid metabolism are probably related to those in carbohydrate metabolism since it is likely that the transfer of energy required for fat synthesis is derived mainly from coupled reactions involving the simultaneous oxidation of some normal carbohydrate intermediate.[36] Thus, the diabetic state is accompanied by a severe loss of ability to synthesize fatty acids from glucose, lactate, and pyruvate.[37, 38] There appears to be a deficiency in protein synthesis in diabetes, which seems dependent upon glucose utilization.[39] As a result, high fasting plasma amino acid levels are frequently found in patients with severe untreated diabetes.

Using the technic of coronary sinus catheterization in patients with pancreatic diabetes and in dogs made diabetic with alloxan, myocardial glucose consumption was found to be reduced in dogs and man relative to the elevation in blood glucose concentration.[40] Although the diabetic heart can utilize glucose, it does so in relatively diminished amounts. Apparently the heart is not exempt from the most important metabolic defect in diabetes, that of deficient utilization of glucose. Myocardial lactate and pyruvate usage are also diminished. This is in contrast to some of the results obtained on the heart-lung preparation in which an unimpaired utilization of lactate was found.[33] In the intact heart in situ, the reduction in myocardial usage of lactate is so severe that it is primarily

responsible for the reduction in total amounts of energy available from the carbohydrate fraction.[40]

The myocardial extraction of pyruvate is slightly diminished. Although this is statistically not significant, it assumes some importance when one considers that it occurs in the presence of a significant elevation in the arterial concentration of pyruvate. It is likely that there is a metabolic block between pyruvic acid and the tricarboxylic acids, since a diminution of the tricarboxylic acids was found in the presence of essentially normal lactate and pyruvate concentration.[41] Defective phosphorylation of thiamin to cocarboxylase in the diabetic organism may be responsible.[42]

In contrast to the relatively deficient utilization of carbohydrates, the myocardial usage of ketones is slightly increased in the diabetic heart of patients and significantly so in the dog.[40] In the heart of nondiabetic individuals, the aerobic metabolism of ketones accounts for approximately 5 per cent of the total oxygen extraction of the heart. In diabetic patients, this figure is 9.8 per cent.[40] The contribution of ketones to the aerobic metabolism of the diabetic dog heart is 13.5 per cent higher than that of the normal heart.[40] The decrease in the rate of total oxidation of carbohydrates by the heart may have been responsible for the increased myocardial usage of ketones.

There appears to be a relative deficiency of the diabetic heart to utilize amino acids.[40] Normally, a small rise in the arterial amino acid concentration produces a disproportionate increase in the myocardial extraction.[7] In the diabetic man and dog, however, the heart removes a relatively small fraction of amino acids from the coronary blood despite a significant elevation in the arterial concentration.[40] It is likely that this represents a deficiency in protein synthesis, a point of view which is in line with recent work using the incorporation of $C^{14}$ into glutathione and protein fractions.[39]

Using the technic of coronary sinus catheterization, it was found that more than 200 per cent of the total myocardial oxygen extraction of the diabetic human heart can be accounted for by aerobic metabolism of fatty acids.[40] This suggests the likelihood of storage of fatty acids by the diabetic heart. In contrast to the normal heart where storage occurs only when the fatty acid concentration in blood is increased, the diabetic heart appears to store fatty acids at their normal blood concentration. One might speculate that there is some connection between the large myocardial extraction of fatty acids and the disability of the diabetic organism to synthesize them from carbohydrates.[37] Since fatty acids cannot be synthesized and the usage of carbohydrates is limited, their storage represents a stabilizing force to be drawn upon by the heart when the necessity arises. In contrast to this increased extraction of fatty acids by the human heart, the alloxan diabetic dog heart shows no change in fatty acid extraction and utilization.[40]

Insulin fails to increase the usage and extraction of glucose in the diabetic dog's heart.[40] When one considers that in the normal heart utilization of sugar decreases with the decline in arterial glucose concentration, the findings reported demonstrate that insulin increases myocardial glucose utilization. Insulin also fails to increase myocardial pyruvate extraction.[40] On the contrary, the pyruvate concentration in coronary vein blood exceeds that in coronary arterial blood in a number of animals following the injection of insulin. The reason for this observation is not clear, but one may venture the opinion that the pyruvate reversal may be an indication of increased metabolism of endogenous carbohydrate in heart muscle, initiated by rapidly falling blood sugar levels in severely diabetic animals. Under these conditions, the thiamin content of heart muscle may be insufficient for the formation of cocarboxylase. Evidence is lacking for the effect of insulin on myocardial utilization of lactate or fatty acids. However, the hormone produces a significant decline in myocardial usage of ketones.[40]

When compared to results obtained on the myocardial metabolism of non-diabetic man and dogs, the changes appearing in the diabetic heart appear as a broad spectrum of metabolic alterations, probably resulting from varying degrees of interference with glucose utilization. Thus, the diabetic heart is not only deficient

in glucose utilization, but the metabolism of pyruvate and lactate is also affected. In addition, the defect extends to the metabolism of proteins and fats. In the light of the present concept of hyperinsulinism, it is not possible to state whether disturbed insulin enzyme interaction can be explained on the basis of a single mechanism, or whether it is the result of the effect of the hormone on a variety of cellular actions.

### *III. Disturbances in Energy Utilization with Reduced Cardiac Efficiency*

*Cardiac Metabolism in Congestive Failure.* One of the basic phenomena of congestive failure is inadequate ventricular emptying during systole; or, in heart failure, the ratio of the residual volume of the heart to its stroke volume is increased.[43, 44] These are purely mechanical definitions which furnish no information on the etiology of cardiac failure. In some conditions such as beri-beri heart disease and myocardial ischemia, myocardial failure may result from disturbances in energy production and definite changes in myocardial metabolism have been described. Such conditions may be defined as "metabolic failure."

Most information on the human heart in congestive failure has until recently stemmed from work which has endeavored to obtain knowledge of the disturbed mechanisms of the cardiac pump by studying the effect of the action of the pump in the form of cardiac output and pressures. These findings reveal little of the basic disturbance underlying myocardial failure. The information that in most patients with congestive heart failure the cardiac output is decreased, except in patients with high output failure, tells us only that the pump delivers a lesser volume of fluids than it should. It tells us nothing about the basic underlying disturbances within the pump itself.

Knowledge of the degree of cardiac emptying as expressed by the quantity of residual blood in the heart or by the ventricular filling pressure and the shape of the ventricular pressure curve is of greater significance.[20, 43, 44] This is because of the relationship existing between the stretch of the muscle fibers, as expressed in the diastolic volume or the initial tension, and the dynamic and metabolic function of the heart.[45, 46, 47] The relationship between diastolic volume and myocardial oxygen consumption has direct bearing on some of the intrinsic mechanisms of heart failure. As Visscher and Starling state: "The oxygen consumption of the isolated heart maintained at constant chemical and temperature conditions is determined by its diastolic volume and therefore by the initial length of its muscle fibers."[48] This undoubtedly holds for the isolated heart in vitro where the changes in residual volume and the initial tension are acute. However, in clinical heart failure, the oxygen consumption per unit of myocardium is within normal limits although the diastolic volume is increased.[49] The results of studies on the effects of digitalis on the human heart are equally not in line with the findings on the heart-lung preparation.[50] Since digitalis probably diminishes the diastolic volume of the failing heart, it should reduce myocardial oxygen consumption; but the injection of Cedilanid has no effect on the oxygen usage of the failing human heart. When, however, the load of the failing heart increases suddenly, as during exercise, a definite rise in myocardial oxygen consumption is observed.[51] This indicates that the failing myocardium, not unlike the normal heart, responds to an acute increase in load by a rise in aerobic metabolism.

The finding that in failure cardiac work is diminished, while the myocardial oxygen usage remains unchanged, suggests that the failing heart has partially lost its ability to convert energy derived from processes of energy production into useful work. Further support for this hypothesis comes from the observation that the myocardial extraction and usage of substrates appears normal in cardiac failure although cardiac efficiency or reserve is diminished.[9] Coronary sinus catheterization has shown that there is no statistical difference in myocardial usage of glucose, pyruvate, lactate, amino acids, or ketone bodies between the failing and the non-failing heart.[9] One is therefore led to conclude that in congestive failure there is deficient utilization of energy. Reports that the spontaneously failing heart in

vitro retains its normal ATP content and is even richer in phosphocreatine than the non-failing heart point in the same direction.[52] Furthermore, in experiments on extracted heart muscle, changes in work performance can be brought about by alterations in muscle loads with the ATP concentration in the fluid bathing the muscle remaining constant.[52] This illustrates that changes in work can occur without alterations in supply of high energy phosphate.

It appears, therefore, that pathways leading to myocardial failure can start from metabolic disturbances within the myocardium, that is, from processes concerned with energy production, or they can originate in the structures concerned with energy liberation, the contractile protein. Eventually, however, all the roads join and failure of energy liberation is the ultimate result. The cause of this failure in energy liberation may well be in changes within the structure of the contractile proteins of the heart muscle.

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# ABSTRACTS

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## BLOOD COAGULATION

**Hockerts, T. and Mülke, G.: Animal Experiments Concerning the Effects of the Anticoagulant Tromexan on Coronary Circulation and $O_2$ Consumption of the Heart.** Cardiologia **26:** 34 (Fasc. 1), 1955.

The authors studied in anesthetized dogs the effect on intravenous injection of 40 to 80 mg. Tromexan upon blood flow through the right coronary artery, the arterial and venous coronary pressure and oxygen consumption of the heart. In addition, the cardiac output and the blood flow through the femoral artery or femoral vein were recorded. The results were as follows: Coronary blood flow increased whereas arterial and venous pressure and cardiac output remained unchanged. The total oxygen consumption of the heart declined slightly, the arterial oxygen desaturation was unchanged and the saturation of the blood of coronary veins usually increased. It is concluded that Tromexan, applied intravenously, has definite vasoactive effects which are more pronounced in the coronary than in the peripheral circulation.

PICK

**Manning, P. R. and Walford, R. L.: Lack of Effect of Fat Ingestion on Blood Coagulation.** Am. J. M. Sc. **228:** 652 (Dec.), 1954.

The influence of the ingestion of fat as cream or a butter-egg-bacon feeding upon the coagulation time was observed in 18 patients. In addition, the clot retraction and prothrombin consumption were determined. The ingestion of cream was followed by lipemia, the degree of which was correlated with the fat content of the cream samples. The oral ingestion of varying amounts and types of fat had no significant effect upon blood coagulation. The age of the patients did not influence the results. There was no effect observed on clot retraction or on prothrombin consumption times.

SHUMAN

**Nilsson, I. M. and Wenckert, A.: Demonstration of a Heparin-like Anticoagulant in Normal Blood. 1. Human Blood.** Acta med. scandinav., Supplement **297:** 7 (Oct.), 1954.

The authors were stimulated to make the studies reported by the observation that in the course of routine one-stage prothrombin determinations serum clotted more quickly than did plasma. Calcium oxalate is felt to remove a clot inhibitory principle from human blood because: (1) at one and the same ionic strength and final concentration of the clotting mixture citrated blood clots more slowly, and oxalated blood more quickly than whole blood, (2) stored autolyzed blood has less anticoagulant effect if calcium oxalate has been added to it before storage, (3) the calcium oxalate precipitate formed on decalcification of blood with oxalate contains an inhibitory principle as well as prothrombin and (4) Amberlite plasma no longer responds with shorter clotting times on dilution after treatment with calcium oxalate. Prothrombin adsorbing salts other than calcium oxalate were also found to remove an inhibitory principle as well as prothrombin from the blood. In the citrate eluate from adsorbate from human oxalated plasma an anticoagulant as well as prothrombin was recovered. This anticoagulant resembles heparin and is believed to be present in normal human blood in sufficient quantity that physiological significance can be attributed to it. In the citrate eluate prothrombin occurred in association with the anticoagulant and could be activated to thrombin by the removal of the anticoagulant.

ROSENBAUM

## CONGENITAL ANOMALIES

**Dorney, E. R., Fowler, N. O. and Mannix, E. P.: Unilateral Clubbing of the Fingers Due to Absence of the Aortic Arch.** Am. J. Med. **18:** 150 (Jan.), 1955.

The authors report the case of a five year old Negro child with unilateral clubbing of the fingers, due to absence of the aortic arch. The blood supply to the right upper extremity came through the aortic remnant while the left arm and the remainder of the body were supplied through a patent ductus arteriosus which opened widely into the descending aorta. Preoperative cardiac catheterization studies, roentgenograms of the heart with the catheter passing from the right ventricle into the descending aorta are presented in addition to the operative findings.

HARRIS

**Shephard, R. J.: Redistribution of Systemic Blood Flow in Pulmonary Stenosis.** Brit. Heart J. **17:** 98 (Jan.), 1955.

Individuals with pure pulmonary stenosis frequently have normal blood flow and normal arterial oxygen saturation. Yet cyanosis is commonly precipitated by exposure to cold, not sufficient to produce it in the individual with a normal heart. This phenomenon suggests an abnormal distribution of blood. By comparing the relationships of the oxygen saturation of the superior and inferior vena cava to the mixed right ventricular blood in the normal and in the individual with pure pulmonary stenosis, the author deduces that in the latter there is a redistribution of blood with blood flow from the upper half of the body exceeding the normal value of 40 per cent of the cardiac output.

SOLOFF

**Bush, J. A. and Ainger, L. E.: Congenital Absence of the Spleen with Congenital Heart Disease.** Pediatrics **15:** 93 (Jan.), 1955.

The clinical features and hematologic findings as well as the post mortem findings of a case of congenital absence of the spleen of a year old infant are presented. Because the blood findings (target cells, decreased osmotic fragility, H-J bodies, and siderocytosis) in association with findings (cyanosis, clubbing, and cardiac murmurs) suggestive of congenital cardiovascular abnormalities were present, the diagnosis of splenic agenesis was made prior to death. The authors point out the characteristic blood picture of the absence of the spleen, and this picture in an infant with other signs of congenital abnormalities suggests splenic agenesis. Post mortem findings verified the clinical diagnosis.

HARVEY

**Richards, M. R., Merritt, E. K., Samuels, M. H., and Langmann, A. G.: Congenital Malformations of the Cardiovascular System in a Series of 6053 Infants.** Pediatrics **15:** 12 (Jan.), 1955.

A thoughtful and well done study of infants in 5964 pregnancies is reported. Particular attention is paid to the incidence of cardiovascular abnormalities. The infants were carefully studied during the first year of life and subsequently, if doubt still existed after the first year about the presence of an abnormality. There being 86 multiple births, the total studied was 6053 infants. Fifty infants showed a cardiovascular abnormality, an incidence of 0.83 per cent. The incidence rate was higher in the still born group (5.4 per cent) and in those who died within one month of birth (10.2 per cent). Cardiovascular malformations were three times more common in the premature, than in the full term infants. Etiologic factors were considered. The incidence is higher with advancing maternal age and multiparity reaches a peak at the third pregnancy and falls off considerably with subsequent ones. These data submitted to careful statistical evaluation are shown to be significant. Maternal infections during pregnancy were shown not to be a factor in the etiology of these abnormalities, although there were four cases of rubella in the first trimester of pregnancy in the maternal population. It is of interest, but not statistically significant, that three of the mothers who had herpes simplex during the first trimester produced infants with the tetralogy of Fallot. It was shown statistically that no acute or chronic medical conditions in the mothers, nor any complication of the pregnancy per se was a factor in the production of the abnormalities. In the 27 proven cases (verified by operation, or autopsy), the abnormalities were many, including nine abnormalities of the great vessels, five patent ductus arteriosus, five tetralogy of Fallot. It was found that during the first week of life, the physical findings were more of a reliable index of abnormality than chest x-ray films. Both, however, revealed only 50 per cent of the abnormalities which, eventually, during the follow-up period, were brought to light. Associated congenital abnormalities of other organ systems arising from other germ layers were found, but the majority of the other defects did arise from ectoderm. There was a statistically significant association between congenital cardiac abnormalities and those infants who were mongoloids as well as those infants who have diaphragmatic hernias and die in early life.

HARVEY

**Johnson, R. P.: Anomalous Pulmonary Veins: Report of Nine Cases.** Ann. Int. Med. **42:** 11 (Jan.), 1955.

In a series of 100 cardiac catheterizations at Brooke Army Hospital over a period of three years, nine patients were found to have anomalous pulmonary veins. It was the only malformation in five patients (except for one who had a persistent left

superior vena cava); in three patients there was also an atrial septal defect (one with pulmonic stenosis in addition), and one patient had a possible atypical patent ductus arteriosus. This anomaly, therefore, is not rare and must be considered in the differential diagnosis of patients with increased pulmonary blood flow. If it is the cause of disability, the possibility of surgical cure exists. Cardiac catheterization is the best method for detecting this condition. However, as has been pointed out, this procedure is subject to misinterpretation and may result in the erroneous diagnosis of the malformation. This is because the right pulmonary veins empty into the left atrium close to the atrial septum, so that if the catheter tip enters the left atrium through an atrial septal defect, it may immediately pass out into the right lung field, appearing in the fluoroscope screen or roentgenogram similar to cases where the catheter has entered an anomalous pulmonary vein from the right atrium, an appearance, which up until recently was considered pathognomonic of an anomalous pulmonary vein. Angiocardiography, dye dilution curves, and even conventional chest roentgenograms are also useful in the diagnosis.

WENDKOS

**Rosenthal, L.: Coarctation of the Aorta and Pregnancy.** Brit. M. J. **1:** 16 (Jan. 1) 1955.

Five cases of this combination are reported bringing the total to 96. One 25 year old patient was delivered by caesarian section because of the development of precordial pain and tachycardia at the thirty-seventh week. She was well thereafter for five months and then died suddenly. No postmortem examination was performed. A 21 year old patient with coarctation was delivered by Caesarian section because of placenta previa. A 43 year old mother of four children died suddenly, two weeks before the expected date of confinement. Autopsy revealed dissection of the ascending aorta with rupture into the pericardium. There was a bicuspid aortic valve. A 24 year-old, mother of one child, died suddenly at about the twentieth week of her second pregnancy, as a result of rupture of an intracranial aneurysm. Coarctation of the aorta and bicuspid aortic valve were present. A 30 year old primipara died suddenly at the thirty-eighth week of pregnancy. Dissecting aneurysm of the ascending aorta had ruptured into the pericardial sac.

Although the successful termination of multiple pregnancies, 11 in one case, 7 in another are reported, the maternal prognosis is generally poor in coarctation of the aorta with pregnancy. Two instances of successful surgical correction of the coarctation in pregnant women have been reported.

McKUSICK

**Ireland, C. R., Witham, A. C. and Harper, H. T., Jr.: Congenital Heart Disease Among Mental Defectives and an Assessment of Cardiac Survey Methods.** New England J. Med. **252:** 117 (Jan. 27), 1955.

A survey of 723 patients ranging from new-born infants to persons 63 years of age was made in a state institution for mental defectives. The incidence of acquired heart disease was 4.42 per cent and that for congenital heart disease was 2.35 per cent. The incidence of congenital heart disease appeared to be seven times as great as that in mentally normal persons. Seven cases of heart disease were detected by a mass electrocardiographic technic which might have escaped diagnosis by x-ray or clinical survey alone. Fourteen cases would have escaped detection if auscultatory observations had not been made and an additional seven cases were discovered only by measurement of the blood pressure. The frequency of congenital heart disease was seven per cent in the mongoloid patients, the highest incidence associated with any of the specific mental diagnoses. However, this figure was much lower than that of 50 per cent often quoted as the incidence of congenital heart disease in mongoloid patients studied at post-mortem. The authors feel that this figure is not applicable to adults with this condition. The experience with this group suggested that it was impossible to evaluate the pulmonic systolic murmur of moderate intensity which changes with respiration and position without the benefit of electrocardiographic and x-ray methods.

The authors found mass survey x-ray studies an inefficient means of detecting heart disease. Even when the films were deliberately "over-read", only 12 of 45 cases of heart disease were discovered. The 4-lead electrocardiogram (leads I, $aV_F$, a lead between $V_1$ and $V_2$, and a fourth, one interspace above the usual $V_6$) disclosed only 23 of 49 instances of cardiac disease. The combination of radiographic and electrocardiographic methods revealed 28 cases. False-positive interpretations by either method were also common. It was concluded that any survey method which excludes auscultation and blood pressure measurement may well miss almost half the cases of heart disease in the group. Surveying by auscultation presents the problems of the frequency of murmurs without heart disease, the need for x-ray and electrocardiographic study for the evaluation of murmurs, the requisite skill and experience of the examiner and examiner fatigue. These authors found that it was difficult to examine more than 10 or 15 patients in a series without a recess, particularly because of the intense concentration necessary to detect minimal diastolic murmurs.

ROSENBAUM

**Flynn, J. E., Siebens, A. A. and Williams, S. F.: Congenital Absence of a Main Branch of the Pulmonary Artery.** Am. J. M. Sc. **228:** 673 (Dec.), 1954.

A patient referred for study of hemoptysis was found to have an abnormal chest roentgenogram with a shift of the mediastinum to the right and a diminution of the volume of the right lung. Pulmonary ventilatory studies revealed a moderately reduced vital capacity. Bronchospirometry revealed that, although 43 per cent of the ventilation was performed on the right, there was only a negligible uptake of oxygen on this side even when 100 per cent oxygen was breathed. Angiocardiography demonstrated the absence of the right pulmonary artery. Cardiac catheterization disclosed minimal elevation of pulmonary artery pressures. It was impossible to pass the catheter into the right pulmonary artery. It is suggested that enlargement of the bronchial arteries may be responsible for hemoptysis in these cases and may represent an indication for pneumonectomy.

SHUMAN

**Gordon, A. J., Donoso, E., Kuhn, L. A., Ravitch, M. M. and Himmelstein, A.: Patent Ductus Arteriosus with Reversal of Flow.** New England J. Med. **251:** 923 (Dec. 2), 1954.

The case of a young woman with a patent ductus arteriosus and reversal of flow, observed from the age of 10 to death during an operation at the age of 25, is reported. The diagnosis was established by clinical, angiocardiographic and cardiac catheterization studies. Differences in cyanosis between the two hands and between the upper and lower extremities were easily seen. Prior to operation the oxygen content of blood from the right radial artery was 17.4 vol. per cent (71.9 per cent saturated), whereas that from the right femoral artery was 13.3 vol. per cent (54.9 per cent saturated). During angiocardiography the ductus arteriosus was visualized and there was dense opacification of the descending aorta 1½ seconds after the injection with some opacification of the aortic arch, right innominate and left brachiocephalic vessels apparently due to reflux of the contrast material. Death at operation resulted from ventricular tachycardia and fibrillation with alterations of the heart action beginning before the ductus ligated. Postmortem study disclosed advanced atherosclerosis in the larger intrapulmonary arteries, extreme narrowing of the smaller intrapulmonary arteries with intimal proliferations and fibrinoid deposits and some points of complete obliteration of the lumen associated with destructive medial alterations. The authors feel it impossible to state the age at which the right-to-left shunt began in this patient. Electrocardiograms at the age of 10 years showed right axis deviation. At 22 years, when the femoral-artery blood was 78 per cent saturated with oxygen, there was only faint cyanosis of the nailbeds of the finger.

The authors believe that closure of the ductus should be attempted in these cases. They do not agree with the concept that the patent ductus serves as a vent to the output of the right side of the heart in these cases. It is suggested that the ductus be closed slowly with technics available for venous bleeding, application of tourniquets and arterial transfusion, as well as other supportive measures, if closure of the ductus results in excessive stress upon the right ventricle or fall in the systolic blood pressure.

ROSENBAUM

**Barndo, J. L., Nades, A. S., Rudolph, A. M., and Neuhauser, E. B. D.: Atrial Septal Defects in Children.** Pediatrics: **14:** 618 (Dec.), 1954.

Clinical features and physiological data on the circulatory dynamics of 32 children with atrial septal defects are presented. In 21 of these the pathologic proof is clear cut, obtained from either operation or autopsy. The clinical features are basal systolic murmur, fluoroscopic hilar dance, absence of left auricular enlargement, and incomplete right bundle branch block. All patients were shown to have a left-to-right shunt with considerable increase in pulmonary flow, but normal pulmonary pressure and pulmonary vascular resistance. Indications for operative repair are the evidences of large shunts, congestive failure, marked exercise intolerance, marked cardiomegaly alone, or underdevelopment. Of this group, nine children were operated. The operative mortality was 30 per cent. The six children who are presently alive had some increase in exercise tolerance, disappearance of murmurs and decrease in heart size. Electrocardiographic patterns are unchanged.

HARVEY

**Glenn, W. W. L. and Patino, J. F.: Circulatory By-Pass of the Right Heart. 1. Preliminary Observations on the Direct Delivery of Vena Caval Blood into the Pulmonary Arterial Circulation. Azygos vein—Pulmonary Artery Shunt.** Yale J. Biol. & Med. **27:** 147 (December), 1954.

The surgical treatment of certain congenital anomalies characterized by non-function of the right atrium or ventricle may depend upon the delivery of vena caval blood into pulmonary arterial circulation. It has been estimated that in the human a mean pressure of about 13 to 17 mm. Hg would be required to maintain a normal flow through the pulmonary artery. A venous pressure of this magnitude would probably not cause edema, though it would lead to varicosities and growth of collaterals.

The authors describe their technic of anastomosing the azygos vein to the right pulmonary artery and then ligating the superior vena cava at its entrance to the heart. This procedure was carried out on nine dogs. Superior vena caval pressures after the establishment of the shunt varied from 118 to 250 mm. saline. Angiocardiograms demonstrated the passage of dye into the right pulmonary arterial circulation.

These preliminary experiments show that at least some blood from the superior vena cava passes through the right lung. It is possible that pulmonary arterial resistance may fall after prolonged exclusion of the pulmonary artery from direct continuity with the heart. By-pass of the right heart might be expected to benefit conditions such as tricuspid or pulmonary atresia, Ebstein's anomaly, bilocular heart, transposition of great vessels, and perhaps Eisenmenger's complex.

ENSELBERG

**Rudolph, A. M., Nadas, A. S., and Goodale, W. T.: Intracardiac Left-to-Right Shunt with Pulmonic Stenosis.** Am. Heart J. **48:** 808 (Dec.), 1954.

The clinical features of 10 children, seven females and three males, with moderate pulmonic stenosis and left-to-right intracardiac shunt are reviewed. Six had atrial defects, three ventricular defects, and one an *ostium auriculoventriculare commune*. Studies of the estimated blood flows revealed systemic blood flows within normal range in all cases. The pulmonary blood flows were larger than the respective systemic flows due to left-to-right shunting of blood. A significant mean systolic pressure gradient between the right ventricle and pulmonary artery was demonstrated in all cases ranging from 15 to 49 mm. Hg. In some instances, it was suggested that the nature of the pulmonic stenosis is relative to enlargement of the right ventricle and pulmonary artery. In large left-to-right shunts, the authors state that closure of the defect may be advisable and the mild pulmonic stenosis should not deter surgical elimination of the shunt.

RINZLER

**Maxwell, Jan and Wilson, R.: Cor Pulmonale in Infancy Simulating Congenital Heart Disease.** Pediatrics, **14:** 587 (Dec.), 1954.

Two cases of cor pulmonale in infants under one year of age are presented. The clinical features of these cases, the authors believe, permit differentiation from congenital heart disease. The children appear normal at birth but in a few months develop easy tiring, failure to maintain weight and mild cyanosis. The clinical findings and electrocardiogram show right sided hypertrophy and preponderance. The anatomic cause of the cor pulmonale revealed at autopsy was an apparent change in the pulmonary circulation. In one instance, medial hypertrophy of the muscularis coat occurred in widespread fashion throughout the whole pulmonary tree; in the other case there was an arteriolititis with minute thrombi in the arterial tree of the right lung only. A discussion is presented upon possible causes for these pathological changes.

HARVEY

## CONGESTIVE HEART FAILURE

**Baschieri, L., Ciampalini, L. and Guidi, P. L.: Antidiuretic Effects Following Oxygen Therapy in Congestive Heart Failure.** Cardiologia **26:** 42 (Fasc. 1), 1955.

In three cardiac patients with oliguria, two controls and two patients with liver cirrhosis and ascites, the effect of oxygen therapy on diuresis and excretion of antidiuretic factors in the urine was investigated. In addition, the effect was studied of an antidiuretic hormone preparation (Tonephin) with or without concomitant Oxygen therapy.

In the cardiac patients $O_2$ application increased the diuresis in contrast to the controls and the patients with liver disease. The urine of the cardiac patients contained increased amounts of antidiuretic substances which were reduced to below normal by $O_2$ treatment. Furthermore, in the cardiac patients, injection of the antidiuretic hormone resulted in a far more pronounced drop of diuresis than in the controls, and this too was partially counteracted by Oxygen.

It is concluded that in cardiac patients with oliguria, the increased content of antidiuretic substance in the urine is probably due to increased excretion of posterior pituitary hormone and to its inadequate inactivation in the peripheral tissues. The diuretic effect of oxygen treatment in such cases is attributed to inhibition of secretion and increase in peripheral inactivation of the antidiuretic hormone.

PICK

**Schwartz, W. B., Relman, A. S. and Leaf, A.: Oral Administration of a Potent Carbonic Anhydrase Inhibitor ("Diamox"). III. Its Use as a Diuretic in Patients with Severe Congestive Heart Failure Due to Cor Pulmonale.** Ann. Int. Med. **42:** 79 (Jan.), 1955.

Seventeen patients hospitalized because of severe congestive failure due to cor pulmonale were treated with Diamox. A large diuresis and corresponding clinical improvement were observed in approximately half the trials, with an average weight loss of 15.5 pounds in five to 12 days of treatment. The remaining cases lost little or no weight and showed no clinical improvement. Most patients became slightly more acidotic as the result of treatment. The partial pressure of carbon dioxide in the blood usually did not change significantly. The only difference noted between the responsive and unresponsive groups appeared to be the initial level of blood bicarbonate, which was slightly higher in the patients who responded to treatment. In the patients who had a diuresis, loss of bicarbonate appears in some manner to have allowed renal excretion of chloride despite low plasma chloride levels. Explanation of this phenomenon must await further elucida-

tion of the mechanisms regulating renal tubular transport of chloride. In any event, it is probable that chloride loss prevented more rapid reduction in plasma bicarbonate and thereby enabled these patients to continue their diuresis for several days. It has been previously shown that without chloride loss, the bicarbonate diuresis is rapidly self-terminating and patients soon become refractory to continued treatment as the plasma bicarbonate level falls. In the present study, administration of Diamox at intervals throughout the day appeared to be a satisfactory dosage schedule; however, there are insufficient data to indicate what the optimal regime might be.

WENDKOS

**Batterman, R. C., Grossman, A. J., Schwimmer, J., and Blackman, A. L.: Treatment of Congestive Heart Failure and Anginal Syndrome with Choline Theophyllinate.** J.A.M.A. **157:** 234 (Jan. 5), 1955.

Forty-five patients with congestive heart failure and 32 patients with the anginal syndrome were treated with choline theophyllinate (Choledyl). Improvement in congestive heart failure patients, consisting either of removal of the need for mercurial diuretics or decreased need for mercurial diuretics, was noted in 62 per cent. Satisfactory relief and control of the anginal syndrome occurred in 23 of 32 patients (or 72 per cent). Because of the high predictability of therapeutic response to this medication, the absence of gastro-intestinal irritation, and the low likelihood of the development of tolerance, it is suggested that choline theophyllinate is an effective and safe xanthine with none of the disadvantages that may be encountered with aminophyllin or other theophylline salts.

KITCHELL

**Alzamora-Castro, Battilana, G., Garrido-Lecca, G., Rubio C., Abugattas, R. and Bouroncle, J.: Acute Left Ventricular Failure and Carotid Sinus Stimulation.** J.A.M.A. **157:** 226 (Jan. 15), 1955.

In 1947 the authors observed that massage in the region of the carotid sinus could stop or improve rapidly the acute crisis of pulmonary edema in persons with arterial hypertension. Since then the procedure has been used routinely in this type of case and frequently the results have been excellent. Unilateral massage is applied over the carotid sinus region by moving the thumb firmly under the anterior border of the sternocleidomastoid muscle. The pressure over the carotid sinus in some patients is continued for as long as half an hour. When the reflex becomes exhausted on one side, a good response is often obtained on the opposite side. The response is considered effective when cardiac rate and blood pressure decrease to normal. In order to avoid accidents and overeffects, the intensity of the pressure on the carotid sinus is controlled through auscultation of the heart and frequent blood pressure readings. This method produces a rapid improvement in hypertensive patients with acute pulmonary edema or cardiac asthma and will considerably shorten the recovery period in the same type of patient after standard exercise tolerance tests.

KITCHELL

**Moyer, J. H., Miller, S. I. and Snyder, H.: Cerebral Hemodynamics in Patients with Heart Failure Associated with Hypertension and the Response to Treatment.** J. Clin. Invest. **34:** 121 (Jan.), 1955.

Cerebral hemodynamics were studied by the nitrous oxide method in 20 patients with hypertension complicated by heart failure. Cerebral blood flow and oxygen consumption were not altered. Likewise, rapid digitalization did not alter cerebral hemodynamics.

Cerebral blood flow was somewhat depressed in six other patients with failure and aortic insufficiency or mitral stenosis. However, this reduction may be due to the mechanical alterations resulting in a depressed cardiac output and not to congestive failure per se. In severe cardiac failure with dyspnea due to severe pulmonary congestion, accurate blood flow determinations by this technic are not possible.

WAIFE

**Lilienfield, L. S., Freis, E. D., Partenope, E. A. and Morowitz, H. J.: Transcapillary Migration of Heavy Water and Thiocyanate Ion in the Pulmonary Circulation of Normal Subjects and Patients with Congestive Heart Failure.** J. Clin. Invest. **34:** 1 (Jan.), 1955.

Transcapillary loss was measured by injecting a non-diffusible dye (T-1824, Evans blue) and the substance studied (deuterium oxide, $D_2O$ and thiocyanate ion) into an afferent vessel of an organ and sampling from an efferent vessel during the first circulation. The difference between the expected concentration of the diffusible substance, as indicated here by the dye, and that experimentally determined is a measure of transcapillary loss.

It was found that deuterium oxide freely and rapidly passed through pulmonary capillary walls, but the curve differed markedly from that of the forearm and indicated a small pulmonary extravascular tissue space. This extravascular water space averaged 190 cc. in the lungs of normal subjects, but 290 cc. in patients with congestive failure.

The lung capillaries were relatively impermeable to thiocyanate ions as compared to forearm capillaries.

WAIFE

**Hulet, W. H., The Sodium, Potassium and Chloride Content of the "200 mg Sodium Diet."** Am. J. M. Sc. **229:** 85 (Jan.) 1955.

Thirteen separate menus prepared by a metabolic kitchen each constructed to contain 200 mg. of sodium and providing 70 Gm. of protein with calories ranging from 1900 to 2300, were analyzed for their electrolyte composition by a method described by the author. In addition, a sample menu of the Kempner rice and fruit diet was prepared for analysis. In the preparation of the diets the tables of Bills and associates were employed. In the group of 13 diets analyzed, the actual sodium content was found to range from 304 to 812 mg. with an average of 513 mg. The Kempner diet was found to have 169 mg. rather than the 29 mg. expected. It is suggested that the actual determination of the sodium content of diets is required since there is some doubt as to the validity of the tables used for computing these values.

SHUMAN

**Webb, W. R., and Campbell, G. D. Use of the Endotracheal Tube in Pulmonary Edema.** J. Thoracic Surg. **28:** 222 (Sept.), 1954.

Regardless of the etiology of the pulmonary edema, whether cardiac, anoxic or toxic, one common factor, partial or complete obstruction by the edema fluid, quickly develops. If these patients die, it is usually by drowning. Yet nearly all reported medical regimen overlook the important possibility of mechanically removing the edema fluid. As a result of the ensuing bronchial obstruction, there develops a variable degree of anoxia. Anoxia causes both pulmonary-artery hypertension and capillary dilatation leading to congestion, stasis, mucosal edema, and further transudation of edema fluid with increased obstruction and greater anoxia. It seemed extremely important to interrupt this cycle at some point, and the mechanical removal of the accumulating transudate appears to be the most feasible and rewarding.

The authors inserted an endotracheal tube with an inflatable cuff into the trachea with the patient still asleep or under local anesthesia, if he is awake. Oxygen is administered under a positive pressure of 5 or 6 cm. of water. Brief periods of suction through the endotracheal catheter with a smaller urethral catheter are repeated as frequently as may be necessary. The authors at times had to suction a patient as often as once each minute and found that, with a little practice, it is quite possible to discontinue the positive pressure oxygen for only about five seconds during each aspiration. In addition, all the usual adjunctive measures have been used including intravenous digitalis and aminophyllin, restriction of fluids, mercurial diuretics, rotating tourniquets on the extremities, and actual phlebotomies. The authors present four cases where this technic was employed successfully. One patient died on the third postoperative day.

The authors point out the large part anoxia plays in the precipitation of pulmonary edema. The oxygen given under pressure combats bronchospasm and mucosal edema as well as directly increasing the intra-alveolar pressure which helps prevent transudation of fluid from the capillaries into the interstitial tissues of the lungs. In addition, the increased pressure retards pulmonary blood flow, thereby reducing the pulmonary capillary blood pressure. Positive pressure oxygen should not be used in the presence of shock.

It has been clearly demonstrated that the endotracheal tube can be left in place for a period of days without causing great tracheal or laryngeal damage. It is the authors preference, if the tube is to remain in place longer than forty-eight hours, to perform a tracheotomy which is much more satisfactory for removing the crusted secretions that inevitably seem to form.

DENNISON

**Danzig, L. E., and Gomez, A. C.: Long-Term Intravenous Use of Arfonad on the Treatment of Pulmonary Edema.** Am. J. M. Sc. **228:** 626 (Dec.) 1954.

Arfonad is a ganglion blocking agent which has an effective blood pressure lowering effect probably through direct peripheral vasodilation as well as through ganglion blockade. In this report, the drug was administered intravenously for a total of 11 days to a patient with chronic glomerulonephritis complicated by hypertension and pulmonary edema. During the treatment period, the blood pressure decreased, and the signs and symptoms of pulmonary edema subsided. The hypotensive effects were readily controlled by regulation of the infusion rate. Tolerance of the drug did not develop and untoward reactions were minimal. The latter effects consisted of photophobia due to fixed pupillary dilatation and a fall of the basal body temperature. The urinary volume was not increased and the patient became more uremic and acidotic; death occurred following cardiac arrest.

SHUMAN

## CORONARY ARTERY DISEASE

**Graybiel, A.: The Intermediate Coronary Syndrome.** Armed Forces M. J. **6:** 1 (Jan.), 1955.

The *intermediate coronary syndrome* is the name given by Graybiel to a syndrome of coronary artery disease which differs from that of angina pectoris in pain characteristics, and in other features from myocardial infarction. The pain in this syndrome lasts longer than a few minutes after the precipitating factors are no longer present and after nitroglycerin; furthermore, the pain often arises spontaneously and is not intimately related to effort.

There are few other symptoms; the physical examination is usually negative. There is little if any evidence of circulatory failure or systemic effects.

Depression of RS-T segments and lowering or inversion of the T waves may be seen, but these changes are transitory. The clinical course ends either in apparent recovery or in the development of infarction. The term "coronary insufficiency" resembles but is not identical with this term.

WAIFE

**Teng, H. C. and Heyer, H. E.: The Relationship between Sudden Changes in Weather and the Occurrence of Acute Myocardial Infarction.** Am. Heart J. **49:** 9 (Jan.), 1955.

An analysis of the relationship between the sudden changes in weather and the onset of cases of acute myocardial infarction was made in three Dallas hospitals, comprising a series of 1,386 patients admitted during a five-year period from 1946 to 1951. An increased frequency of occurrence of acute myocardial infarction was noted during periods of sudden inflows of polar and of tropical air masses. It appears from the present study that sudden meteorologic changes exert an adverse effect on patients with coronary artery disease.

RINZLER

**Sewell, W. H. and Koth, D. R.: Experimental Coronary Occlusion Using a Polyethylene Tube: A Preliminary Report.** Yale J. Biol. & Med. **27:** 187 (Dec.), 1954.

A method is described for producing gradual coronary occlusion and subsequent myocardial infarction in dogs. Such a technic would provide a better base for various experimental surgical studies of methods for "revascularization" of the heart. The method consists of inserting a small piece of polyethylene tubing into the anterior descending coronary artery. The tubing clots over in about three to six hours, as judged by electrocardiographic evidence, and is complete in about 24 to 30 hours as judged by postmortem study.

The authors had no operative mortality after the technique was mastered, and found a much lower late mortality than would have been expected after acute ligation. Myocardial infarcts were uniformly produced. Ventricular fibrillation was uncommon. The mechanism of protection against ventricular fibrillation is not clear. Possibly vasomotor tone in existing collateral channels is relaxed when coronary occlusion is gradual.

ENSELBERG

**Beckwith, Julian R., Kernodle, Dwight T., LeHew, Allen E. and Wood, J. Edwin, Jr.: The Management of Myocardial Infarction with Particular Reference to the Chair Treatment.** Ann. Int. Med. **41:** 1189 (Dec.), 1954.

The series consisted of 80 consecutive admissions to the hospital of patients with acute myocardial infarction who had lived 24 hours or more. All patients were given an anticoagulant, Dicumarol or Tromexan, and prothrombin time determinations were performed once or twice daily. All patients remained in the hospital for 28 to 38 days. They were given morphine or Demerol to control pain and were placed on a diet limited in calories. Patients, who were treated in a chair, are referred to herein as "Up Patients", and those confined to bed as "Down Patients." The Up Patients were allowed in a chair for increasing lengths of time from the second to the fifth day after the infarction. No patient was allowed up until shock, if present, had been controlled or pain had almost disappeared. The Down Patients were kept in bed for 28 days and were not allowed to bathe, shave or feed themselves until the second week after the infarction. They were encouraged to flex and extend their feet frequently, and several were allowed use of a bedside commode once daily. Three of the 39 Up Patients and six of the 41 Down Patients died, a mortality of 7.7 per cent and 14.7 per cent respectively. The two groups were reasonably comparable as to age and severity. The chair treatment apparently did no harm and seemed to be attended by psychologic and physical benefits.

WENDKOS

**Master, A. M., Jaffe, H. L., Teich, E. M., and Brinberg, L.: Survival and Rehabilitation After Coronary Occlusion.** J.A.M.A. **156:** 1552 (Dec. 25), 1954.

The authors report a follow-up study of 500 patients who have survived coronary occlusion for from one to 29 years, and find that two out of every five patients made a complete functional recovery. A similar number made a satisfactory recovery in that they experienced only mild angina or dyspnea on exertion. Three-quarters of these patients were working. Over half the patients have survived more than five years after the initial attack; one out of every five survived the attack for more than 10 years. Among the patients making complete, or satisfactory, recovery, only one out of every five died and this was usually the result of another coronary occlusion or congestive failure. The most reliable gage of recovery after coronary occlusion is the absence of cardiac symptoms, regardless of whether the patients have large hearts, marked electrocardiographic changes or even ventricular aneurysm. On the other hand, when physical examination and laboratory studies are normal, the patient has almost always made an excellent recovery and his outlook is good. Evidently the site of the infarction does not affect the prognosis; the outlook is somewhat better in a younger patient. The patient and the physician should be optimistic about the prognosis of coronary

occlusion, both during the attack and afterward. In this series the outlook of the patients who returned to work was at least as good as it was in those who retired. For this reason, the medical profession should take the lead in acquainting the public with these facts and should enlist the cooperation of business and of social agencies in placing the cardiac patient in industry.

KITCHELL

**Moritz, A. R.: Trauma, Stress, and Coronary Thrombosis.** J.A.M.A. **156:** 1306 (Dec. 4), 1954.

It is true that trauma and its complications may damage the heart, and it is equally true that cardiac disability may develop after injury even though there is no causal relationship between the two events. Workmens' Compensation laws that prevail throughout most of the United States make it important to differentiate between these two whenever the injury is occupational in nature. The various kinds of direct injury to the heart that may result from trauma to the thorax are discussed under the headings of commotion (cardiac shock), myocardial contusion, laceration of the heart, laceration of parietal pericardium, valvular avulsion, and coronary artery contusion. In the absence of direct injury to the heart or thorax, exertion, pain, fear or anger may cause a pressor reaction which, in the presence of coronary atherosclerosis, may lead either to hemorrhage into atheroma or relative coronary insufficiency. Either of these two may lead to immediate cardiac arrest, delayed thrombosis, immediate transient or persistent evidence of myocardial ischemia; or may go on to transient dilatation with recovery on rest. Evidence from postmortem examinations of persons who have died violent deaths indicates that coronary thrombosis is rarely the direct result of trauma. The contention that such was the case is probably never tenable unless supported by facts obtained through postmortem examination. In the presence of coronary atherosclerosis, various secondary effects of trauma or stress are probably capable of either inducing a state of coronary insufficiency or of causing the heart to fail by imposing an excessive work load on it.

KITCHELL

## ELECTROCARDIOGRAPHY

**Evans, W.: The Distinctive Electrocardiogram of Coronary Arteriospasm.** Brit. Heart J. **17:** 15 (Jan.), 1955.

Of 1370 individuals with pain of cardiac origin, 10 were found whose electrocardiograms showed transient inversion of the T waves in $CR_1$ to $CR_4$ and often beyond this lead. This mutable electrocardiogram is ascribed to spasm of the left coronary artery distal to the circumflex branch and proximal to the left marginal branch unless this branch takes origin from the left circumflex. Exercise may reproduce this deformity. The author attaches a favorable prognosis to this syndrome.

SOLOFF

**Den Boer, W., Burger, H. C., and Van Milaan, J. B.: Vectorcardiograms of Normal and Premature Beats in Different Lead Systems.** Brit. Heart J. **17:** 1 (Jan.), 1955.

The authors have previously demonstrated a lack of correspondence of vectorcardiograms registered with different lead systems. By using three different lead systems in 16 individuals with premature beats, they demonstrate that there is no constant relationship between the vectorcardiograms of the normal beats and that of the premature beats. Such a lack of correspondence is attributed to local factors such as an uneven distribution of adipose tissue around the heart.

SOLOFF

**Levit, S. M., and Dinman, B. D.: Effect of Eating on Electrocardiograms After Myocardial Infarction.** J.A.M.A. **157:** 122 (Jan. 8), 1955.

Changes have been frequently observed in the electrocardiograms of normal persons made after the ingestion of food. Twenty-seven consecutive cases with clinical and electrocardiographic diagnosis of acute myocardial infarction were studied before and after food ingestion. All tracings were made with the patient recumbent, and the positions of the precordial leads were carefully marked on the chest so that comparable leads were obtained in the repeated electrocardiograms on the same patient. The postmeal electrocardiograms were obtained a half hour after eating. Change in the polarity of the T wave was classified as a major alteration and variation in magnitude of the T wave without polarity alteration was classified as a minor change. The other components of the electrocardiogram were not significantly affected. Major T wave changes were noted in 10 of the 27 patients studied and very frequently such change appeared in several leads of the electrocardiograms in these 10 patients. The findings suggest there should be a modification of current electrocardiographic technique to obviate the effects of eating, and ideally serial electrocardiograms should be performed in the fasting state; at least several hours should be allowed to elapse between the taking of a meal and the taking of the electrocardiogram.

KITCHELL

**Klepzig, H., Doll, E. and Reindell, H.: The Vectorcardiogram and Precordial Electrocardiogram and Their Dependence on Intracardiac Pressure Values in Right Heart Strain.** Ztschr. f. Kreislaufforsch. **44:** 36 (Jan.), 1955.

The authors compared vectorcardiograms with scalar electrocardiograms (including precordial leads $V_{3R}$ through $V_6$) in 18 patients with right

ventricular strain (proven by cardiac catheterization), 10 normals (1 catheterized), 5 athletes (2 catheterized) and 8 patients with right bundle branch block without clinical evidence for right heart strain.

There was no definite correlation between the shape and direction of the vector loop and the right ventricular pressure. Abnormalities in the beginning of the vector loop consisting in deviation to the left were found only in cases with right heart strain, and this in 80 per cent of cases in which the right ventricular pressure was more than twice of normal. The direction of the rotation of the horizontal loop could be determined correctly in 85 per cent from the precordial electrocardiogram.

This study, according to authors, failed to reveal any vectorcardiographic signs of right heart strain which were not evident in the customary electrocardiogram. However, the interpretation of the vectorcardiogram proved simpler than that of the electrocardiogram.

PICK

**Kühns, K.: The Influence of the Potassium Ion on the Electrocardiogram and the Duration of the Systole.** Ztschr. f. Kreislaufforsch. **44:** 5 (Jan.), 1955.

The authors produced in dogs pretreated by DOCA, elevation of blood potassium levels by massive infusion of potassium solutions, and reduction of potassium levels by infusion of sodium solutions. Electrocardiographic alterations occurring during these experiments were correlated with the potassium and sodium concentrations in the heart muscle and serum.

There was no consistent relationship between the electrocardiographic alterations on one hand and the absolute intracellular or extra-cellular amount of K or Na in the heart on the other hand. However, a definite relationship could be established to the gradient between intracellular and extracellular K concentration. In normal dogs the ratio intracellular to extracellular concentration of K (termed by the authors cardiac potassium quotient) is between 25 and 32. Reduction of this quotient by increase in serum potassium produced typical hyperkalemic changes in the electrocardiogram disappearance of P and increase in T waves, impairment of A-V and intraventricular conduction and development of idioventricular rhythms with progressive slowing terminating in cardiac sandstill. An increase of the quotient, usually corresponding to reduction of the serum potassium, caused in the electrocardiogram augmentation of P waves and P-R intervals, reduction of T waves and depression of the S-T segment. Under both circumstances the Q-T duration became prolonged and the duration of the mechanical systole (the distance from Q to the second heart sound) was shortened.

These experiments can explain clinical observations of hyperkalemic alterations of the electrocardiogram in the presence of normal potassium level as well as the absence of the electrocardiographic alterations in the presence of severe hypopotassemia.

PICK

**Giraud, G., Latour, H., and Puech, P.: Electrocardiography of the Sinus Coronarius. Part II. Study of Endocavitary Electrocardiograms of Dysrhythmias of the Coronary Sinus Origin in Man.** Arch. mal. coeur **47:** 1008 (Dec.), 1954.

In the course of intended or fortuitous introduction of a cardiac catheter into the coronary sinus, disturbances in the origin of the cardiac impulse were observed and recorded in simultaneous peripheral and intracardiac leads. The P waves became inverted in leads II, III and $V_6$, and changed from diphasic to inverted in the cavitary lead, with little or no shortening of P-R, whenever the tip of the catheter was at the entrance into the coronary sinus or at the beginning of the great posterior coronary vein. These changes in contour, ascribed to origin of the impulse in tissues surrounding the coronary sinus, were recorded in form of sporadic premature beats, of bigeminy, or of transient and persistent ectopic rhythms. Transitional complexes between the two types of P waves could be attributed to auricular fusion beats from simultaneous operation of the sinus and ectopic pacemaker or to wandering of the pacemaker from the sinus node to the area of the coronary sinus and vice versa. Transient upward displacement of the S-T segment was sometimes seen in the course of coronary sinus catheterization with or without simultaneous P wave alterations. This can be explained either by accentuation of a TP directed opposite to the inverted P, or to transitory posterior wall ischemia following occlusion of the main venous channel by the catheter.

PICK

**Effert, S., Drewes, J. and Loogan, F.: Electrocardiographic Observations during Cardiac Surgery.** Arch. f. Kreislaufforsch. **21:** 296 (Dec.), 1954.

Continuous electrocardiographic recordings during surgery on 40 cases of pulmonic stenosis, one case of aortic stenosis and 6 cases of mitral stenosis are reported. In all, the opening of the valvular ostium was achieved by a transventricular approach. Thoracotomy and incision of the pleura were followed by insignificant disturbances of rhythm. Instillation of novocaine into the pericardium caused transient abnormalities of the T waves, ascribed to alterations of the superficial layers of the ventricular myocardium. Mechanical stimulation, such as infiltration of the myocardium by novocaine and application of ligatures, produced premature ventricular systoles originating in the area of manipulation. Runs of such ectopic beats and rapid ectopic rhythms were usually recorded at the time of the

actual valvotomy. However, antecedent novocaine infiltration seemed to prevent persistence of the ectopic beats into the post-operative period. In addition to these abnormalities, the procedure usually caused the appearance of intraventricular conduction defects and positional contour alterations caused by the handling of the heart. Contour alteration of the electrocardiogram occurring subsequent to surgery are mostly due to the development of a pericarditis. An instance is illustrated of successful resuscitation in which ventricular fibrillation developing during the operation was abolished by cardiac massage.

PICK

**Rothman, S., Gerlach, E., Prinzmetal, M., Rakita, L. and Borduas, J. L.: Studies on the Mechanism of Ventricular Activity. XIII. Genesis of the Depolarization Complex in the Mammalian Heart.** Am. J. Physiol., **179:** 557 (Dec.), 1954.

Epicardial, intramural, cavity and septal leads were used to study depolarization in normal dog ventricles. The commonest type of epicardial complex was an RS wave with a notch on the initial upstroke. All epicardial leads were observed to have an S wave of variable size following the R wave. The size of epicardial R and thickness of ventricular myocardial were not correlated. Cavity and leads from inner layers were observed to have pure QS waves on the left side and either rS or QS on the right. Records from the inner third of the wall occurred almost simultaneously with those from the cavity. Subendocardial depolarization had only a minor or no effect on the EKG. Middle and outer layers of both ventricles produced R waves with distinct intrinsic deflections. These R waves were produced progressively later in time passing from mid-myocardium to epicardium. Depolarization of middle and outer myocardial layers is apparently responsible for R waves recorded from both ventricles. Outer layers depolarized more slowly than middle. Base was slower than apex. Later epicardial depolarization at the base depended on slower depolarization in outer layers rather than on a greater thickness of myocardium at this point. On the right side the inner myocardial layers depolarized almost simultaneously. However, middle layers were depolarized rapidly and outer layers more slowly at rates which could be measured.

OPPENHEIMER

**Gross, D.: Quantitative Estimation of Ventricular Strain in the Limb Leads.** Am. Heart J. **48:** 881 (Dec.), 1954.

This paper introduces a new empiric formula which expresses in a single equation the opposite changes of the QRS complex and T wave in limb leads I and III, and which thus permits a quantitative estimation of the intensity of existing ventricular strain. It is $[(R_1 - S_1) - 2T_1] + [S_3 - R_3) + 2T_3]$.

Standard values are established in a group of 100 healthy individuals. The mean was found to be +1.84 with a range from −12.5 to +12.5. In cases of left ventricular strain the index is always positive, with a mean of +47.2 and a range from +32.5 to +79.5. In cases of right ventricular strain the index is always negative with a mean of −27.6 and a range from −20.0 to −40.0. Correlations between the strain index and its components, the QRS and T factors, (leads I and III), and the position of the electrical axis are established as much in normal individuals as in cases of left and right ventricular strain. Their pathophysiologic and clinical aspects are discussed. The strain index expresses in a quantitative manner the intensity of the response of the ventricular musculature to the required overwork, regardless of causative factors. It serves to indicate by a quantitative criterion the presence of ventricular overactivity and permits following and comparing the mentioned changes in different cardiac conditions.

RINZLER

# AMERICAN HEART ASSOCIATION, INC.

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## ANNUAL MEETING AND SCIENTIFIC SESSIONS, OCTOBER 22-28

New Orleans will become the cardiologic capital of the United States for a week beginning Saturday, October 22, when the 31st Annual Meeting and 28th Scientific Sessions of the American Heart Association are held.

Thousands of physicians, research scientists and interested laymen from throughout the nation will have an opportunity to acquaint themselves with the latest developments in every phase of the effort to combat cardiovascular diseases.

### *Important "Firsts"*

The Annual Meeting and Scientific Sessions will be marked by several important "firsts." It will be the first time that the Association's Scientific Sessions will be held in the fall and the first time they are to be conducted independently of any other major medical meeting. It will also be the first time that there will be both commercial and scientific exhibits shown at the Annual Meeting. These exhibits will be displayed at the vast Municipal Auditorium, which will be the scene of the Scientific Sessions and of the programs of the Councils on Community Service and Education and on Rheumatic Fever and Congenital Heart Disease.

The other center of cardiologic interest in New Orleans will be the Jung Hotel. It will be there that such key events as the Annual Meeting of the AHA Assembly, the Staff Conference of Heart Association and the several social gatherings will be held.

### *Scientific Sessions*

Clinical and laboratory developments will be brought to the fore during the Scientific Sessions at the Municipal Auditorium, Saturday, Sunday and Monday, October 22 through 24. The scope of these sessions is indicated by the fact that a total of 338 papers have been offered for possible presentation. This is more than twice the number submitted for presentation at any previous AHA Scientific Sessions. Time will permit presentation of between 95 and 118 of these papers.

### *Lectures and Panels*

In addition to these papers, there will be two special lectures and three panel discussions featured during the Scientific Sessions. The lectures will include the Lewis A. Conner Memorial Lecture (Saturday afternoon) and the George E. Brown Memorial Lecture (Sunday morning). The Conner Lecture will be on *Primary Hypertension*, delivered by George Perera, M.D., Associate Professor of Medicine at the Columbia University College of Physicians and Surgeons, New York City; George Burch, M.D., Henderson Professor of Medicine at the Tulane University School of Medicine, New Orleans, will deliver the Brown Lecture on *Digital Rheoplethysmography*. Dr. Burch will be presented by A. Wilbur Duryee, M.D., New York, Chairman of the Section on Circulation which sponsors the lecture.

The panels will include these subjects: *Aneurysms of the Aorta*, moderated by Edgar V. Allen, M.D., Rochester, Minn. (Saturday morning), *Electrolyte Disturbances in Cardiac and Renal Diseases*, moderated by John Merrill, M.D., Boston (Sunday afternoon) and *The Role of Hemodynamic Data in Determining Operability*, moderated by S. Gilbert Blount, M.D., Denver (Monday afternoon).

### *Honor Dr. Wiggers*

Another highlight of the Scientific Sessions will be the presentation on Saturday afternoon of the Albert Lasker award of the American Heart Association for distinguished achievement in the field of cardiovascular diseases. The award will be made to Carl J. Wiggers, M.D., Professor Emeritus and former Physiology Department Head at Western Reserve

Medical School, Honorary Professor of Physiology at the Frank E. Buntz Educational Institute of Cleveland and Editor of *Circulation Research*, the Association's journal of fundamental studies. Dr. Wiggers, "dean of cardiovascular physiologists" and former President of the American Physiological Society, will be honored for his contributions in the fields of research, teaching and clinical medicine. In 1952, he was recipient of the Association's Gold Heart Award.

*Session Chairmen*

The Scientific Sessions will be divided into general sessions and simultaneous sessions of specialized interest to the various sections and councils. The following will preside at these sessions:

**Clinical Cardiology and Cardiovascular Surgery** (Saturday morning)

*Clarence E. de la Chapelle, M.D., New York, Chairman; Robert L. King, M.D., Seattle, Co-Chairman.*

**Conner Memorial Lecture** (Saturday afternoon)

*Irvine H. Page, M.D., Cleveland, Chairman; E. Cowles Andrus, M.D., Baltimore, Co-Chairman.*

**Simultaneous Session, Clinical Cardiology** (Saturday afternoon)

*Thomas J. Dry, M.D., Rochester, Minn., Chairman; Robert W. Wilkins, M.D., Boston, Co-Chairman.*

**Simultaneous Session, Basic Science and Circulation** (Saturday afternoon)

*Ludwig E. Eichna, M.D., New York, Chairman; William F. Hamilton, M.D., Augusta, Ga., Co-Chairman.*

**Simultaneous Session, Cardiovascular Surgery** (Saturday afternoon)

*Jere W. Lord, Jr., M.D., New York, Chairman; George H. Humphreys II, M.D., Co-Chairman.*

**Clinical Cardiology, Circulation and Basic Science** (Sunday morning)

*Irvine H. Page, M.D., Cleveland, Chairman; Edgar V. Allen, M.D., Rochester, Minn., Co-Chairman.*

**Simultaneous Session, Clinical Cardiology** (Sunday afternoon)

*Emmet B. Bay, M.D., Chicago, Chairman; William H. Bunn, M.D., Youngstown, Ohio, Co-Chairman.*

**Simultaneous Session, Basic Science** (Sunday afternoon)

*Gordon Moe, M.D., Syracuse, N. Y., Chairman; A. Wilbur Duryee, M.D., New York, Co-Chairman.*

**Simultaneous Session, High Blood Pressure** (Sunday afternoon)

*Thomas Findley, M.D., Augusta, Ga., Chairman; Eugene B. Ferris, M.D., Atlanta, Co-Chairman.*

**High Blood Pressure and Clinical Cardiology** (Monday morning)

*George E. Burch, M.D., New Orleans, Chairman; E. Cowles Andrus, M.D., Baltimore, Co-Chairman.*

**Simultaneous Session, Clinical Cardiology** (Monday afternoon)

*A. Carlton Ernestene, M.D., Cleveland, Chairman; John J. Sampson, M.D., San Francisco, Co-Chairman.*

**Simultaneous Session, Basic Science and Circulation** (Monday afternoon)

*Eugene A. Stead, Jr., M.D., Durham, N. C., Chairman; Carl J. Wiggers, M.D., Cleveland, Co-Chairman.*

**Simultaneous Session, Rheumatic Fever and Congenital Heart Disease** (Monday afternoon)

*Bernard J. Walsh, M.D., Washington, D. C., Chairman; J. G. Fred Hiss, M.D., Syracuse, N. Y., Co-Chairman.*

*Business Meetings*

Also of importance to physicians will be the business meetings of the Scientific Council and of its sections and councils. These meetings will choose officers of the various groups for the coming year and also elect members-at-large to the AHA Assembly and Board of Directors. Their times are listed in the schedule printed below.

*Community Service Programs*

Physicians interested in the community health, educational, nutritional and rehabilitation aspects of cardiovascular problems will find particular value in the programs being presented by the Association's Council on

Community Service and Education and by this Council jointly with the Council on Rheumatic Fever and Congenital Heart Disease. The Community Service Program will be presented on Sunday. The problem of *Body Weight and Heart Disease* will occupy the morning. This meeting will be chaired by Herbert Pollack, M.D., New York. Participants in the program will include A. June Bricker, New York; Grace A. Goldsmith, M.D., New Orleans; C. Frances MacKinnon, Chapel Hill, N. C.; Herbert H. Marks, New York; and W. H. Sebrell, Jr., M.D., Bethesda, Md. The panel discussion will be moderated by Martin G. Goldner, M.D., Brooklyn, N. Y.

After a luncheon session during which Martin Cherkasky, M.D., New York, Chairman of the Community Service and Education Council, will report on the community service opportunities of the Association, there will be an afternoon session on *Heart Disease and Rehabilitation*. This will be under the chairmanship of E. A. Irvin, M.D., Dearborn, Mich. Among the participants will be Herman K. Hellerstein, M.D., Cleveland; F. Benedict Lanahan, M.D., Philadelphia; John G. Smith, M.D., Rocky Mount, N. C.; and Paul D. White, M.D., Boston.

### *Rheumatic Fever Discussion*

The joint program of the Community Service and Rheumatic Fever Councils will be given on Monday. Its two main subjects will be *Prevention of Rheumatic Fever* and *The Cardiac Child in School*. The discussion on prevention will be chaired by Edward E. Fischel, M.D., New York. Participants will include Lewis Wannamaker, M.D., Minneapolis, and Gene Stollerman, M.D., Chicago. In the school discussion, Leona Baumgartner, M.D., New York City Commissioner of Health, will act as chairman, and Bernard J. Walsh, M.D., Washington, D. C., will be co-chairman. Other participants will be S. Gilbert Blount, M.D., Denver, and Miss Anna Kalmanowitz, Boston.

### *Assembly Panels and Meeting*

The teamwork between physician and layman which is the basis of the American Heart Association's program as a national voluntary health agency will nowhere be better exhibited than in New Orleans on Tuesday and Wednesday, October 25 and 26. These days will be devoted to the Assembly Panel discussions and to the Annual Meeting of the Assembly, top governing body of the Association. The Assembly Panels on Tuesday will include the following:

**Expenditure of Funds for Community Services**

*Ray E. Trussel, M.D., Flemington, N. J., Chairman; A. Carlton Ernestene, M.D., Cleveland, Co-Chairman.*

**Research**

*Francis Wood, M.D., Philadelphia, and George E. Wakerlin, M.D. Chicago, Co-Chairmen.*

**Heart Association Relationships**

*Maurice Donovan, M.D., Schenectady, N. Y., Chairman; Charles L. Bybee, Houston, Co-Chairman.*

**Personnel**

*Ellison R. Cook III, M.D., Savannah, Ga., and David S. Robertson, Los Angeles, Co-Chairmen.*

**Fund Raising**

*Alan W. Giles, Minneapolis, Chairman; John G. Smith, M.D., Rocky Mount, N. C., Co-Chairman.*

The Assembly meeting on Wednesday morning will hear reports from the previous days panels. These reports will furnish policy and program guidelines for the Association's Board of Directors for the coming year. The meeting will also be marked by the induction of Irvine H. Page, M.D., Cleveland, now President-elect, as President of the Association, as well as by the election of new officers and board members.

### *Social Events*

Although the main emphasis of the Annual Meeting and Scientific Sessions is upon medical, educational and business matters, the social side of this national gathering will not be ignored. Among the outstanding events in this respect will be the AHA Annual Dinner and Dance, Sunday evening at the Hotel Jung.

The dinner will be the occasion for the bestowing of the 1955 Gold Heart Awards, and for an address by the incoming AHA President Irvine H. Page, M.D., Cleveland. Also sched-

IRVINE H. PAGE, M.D.

*Dr. Page assumes the Presidency of the American Heart Association after many years as a leader in its top councils. A prime mover in the organization of the Association's Council for High Blood Pressure Research, Dr. Page has also served as President of the Cleveland Area Heart Society. He currently holds the position of Director of Research at the Cleveland Clinic.*

E. COWLES ANDRUS, M.D.

*Dr. Andrus is completing his term as President of the American Heart Association, but he will continue his outstanding service to the Association when he becomes Chairman of the Scientific Council at the Annual Meeting in New Orleans. Dr. Andrus is Associate Professor of Medicine at the Johns Hopkins University Medical School, as well as Physician-in-Charge of the University's Adult Cardiac Clinic and Consultant in Cardiology at the Walter Reed Army Hospital in Washington, D. C.*

uled are the annual dinner of the Section on Basic Science and the Section on Circulation on Saturday and the Assembly luncheon on Tuesday, at which E. Cowles Andrus, M.D., will be the speaker.

### *'Hospitality Center'*

A 'Hospitality Center' will be set up by the Louisiana Heart Association at the Jung Hotel. The center will provide information on the restaurant, recreational, educational and shopping facilities of New Orleans. Also planned are several tours of special interest to physicians' wives attending the meeting.

### *Registration*

Forms for advance registration for the Annual Meeting and Scientific Session can be obtained from the Association. For those unable to register in advance, registration desks will be set up at the Jung Hotel from 6:00 to 10:00 P.M. on Friday evening, October 21. Registration desks will also be established at the Municipal Auditorium. These will be open from 8:00 A.M. to 5:00 P.M. on Saturday, Sunday and Monday.

### *Non-Members Welcome*

Attendance at the Scientific Sessions is open to non-members as well as to Heart Association members. A moderate registration fee of $3.00 will be charged to non-members. This fee will entitle them to copies of the printed proceedings. Medical students, interns, residents, research workers and nurses will be welcome without payment of the fee. Registration forms, including provisions for reserving hotel space, are still available from the AHA, 44 East 23 Street, New York 10.

### *Mexican Tour*

An eight-day medical tour to Mexico has been arranged to follow the Annual Meeting. The tour will start from New Orleans on Thursday, October 27. Included will be special scientific programs in Mexico City arranged by the National Institute of Cardiology. These programs will be offered on the mornings of October 31, November 1 and November 2. Also on the itinerary will be visits to points of religious, cultural and recreational interest in the Mexico City area. Approximate cost of the tour will be $200 including transportation, hotel and several meals.

In addition, an optional tour to the Pacific Coast resort of Acapulco has been arranged from Thursday, November 3 through Saturday, November 5. Additional details and registration forms can be obtained from the Medical Division of the Association.

### *Full Program and Abstracts*

This issue of Circulation contains the fully detailed proceedings of the Scientific Sessions, including abstracts of most papers submitted for possible presentation at the Sessions, in a special section which follow this regular American Heart Association section.

### The Schedule in Brief

#### *Saturday, October 22*

MORNING

General Scientific Session; Panel on *Aneurysm of the Aorta.* (Municipal Auditorium)

AFTERNOON

Lewis A. Conner Memorial Lecture: Presentation of Lasker Award; Simultaneous Special Sessions; Business Meetings, Sections on Basic Science, Circulation, CV Surgery (Municipal Auditorium)

EVENING

Annual Dinner, Sections on Basic Science and Circulation, Jung Hotel

#### *Sunday, October 23*

MORNING

General Scientific Session; George E. Brown Memorial Lecture; Program of Council on Community Service and Education—*Body Weight and Heart Disease* (Municipal Auditorium)

AFTERNOON

Luncheon, Council on Community Service and Education (Jung Hotel); Panel on *Electrolyte Disturbances in Cardiac and Renal Diseases*; Simultaneous Special Sessions of Section of the Scientific Council; Program of Council on Community Service and Education—*Heart Disease and Rehabilitation* (Municipal Auditorium)

EVENING

Annual Dinner-Dance of the AHA (Jung Hotel)

*Monday, October 24*

MORNING

General Scientific Session; Business Meeting, Scientific Council; Joint Program of Councils on Rheumatic Fever and Congenital Heart Disease and on Community Service and Education (Municipal Auditorium)

AFTERNOON

*Panel on The Role of Hemodynamic Data in Determining Operability*; Simultaneous Special Sessions; Business Meeting, Council on Rheumatic Fever and Congenital Heart Disease (Municipal Auditorium); Business Meeting, Council on Community Service and Education (Jung Hotel)

*Tuesday, October 25*

MORNING

Assembly Panels (Jung Hotel)

AFTERNOON

Assembly Luncheon, Address by Irvine H. Page, M.D.; Assembly Panels (continued)

*Wednesday, October 26*

MORNING

Annual Meeting of Assembly (Jung Hotel)

AFTERNOON

Staff Conference of Heart Associations (Jung Hotel)

*Thursday, October 27*

MORNING

Staff Conference (Jung Hotel)

AFTERNOON

Staff Conference Luncheon; Business Meeting; Workshops on Fund Raising and Public Relations (Jung Hotel)

*Friday, October 28*

MORNING

Staff Conference Workshops, continued (Jung Hotel)

## GRANT APPLICATION DEADLINE IS NOVEMBER 1

November 1 is the deadline for applying for grants-in-aid to be awarded by the Association in support of cardiovascular research during the fiscal year beginning July 1, 1956. This deadline date is one month earlier than it was last year. Full information and application blanks may be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10, N. Y.

## PROGRAM OF HIGH BLOOD PRESSURE COUNCIL MEETING, NOV. 18–19

A two-day scientific program on hypertension and related problems will be presented at the Annual Meeting of the Association's Council for High Blood Pressure Research in Cleveland, November 18–19.

The program has been prepared by a committee under the chairmanship of Thomas Findley, M.D., Georgia College of Medicine, Augusta, Ga. The Scientific Sessions will be chaired by Eugene B. Ferris, M.D., Emory University School of Medicine, Atlanta. The program follows:

*Friday, November 18*

*Integraiion of Splanchnic Circulation in Systemic Hemodynamic Adjustments*, Stanley E. Bradley, M.D., College of Physicians and Surgeons, Columbia University, New York.

*Renoprival Hypertension*, Arthur Grollman, M.D., Southwestern Medical School of the University of Texas, Dallas.

Discussion, led by W. J. Kolff, M.D., Cleveland Clinic, Cleveland.

*Varying Patterns of Blood Pressure Response to Autonomic Blockade; Implications Concerning the Interplay of Neurogenic and Humoral Factors in Control of Vascular Tone*, Albert A. Brust, M.D., and Eugene B. Ferris, M.D., Emory University School of Medicine, Atlanta.

Discussion, led by Harry Goldblatt, M.D., Mount Sinai Hospital, Cleveland.

*The Case for Involvement of Trace Metals in Vascular Disease*, Henry A. Schroeder, M.D., and H. Mitchell Perry, M.D., Washington University School of Medicine, St. Louis.

*Saturday, November 19*

Symposium on *Neurovascular Relationships*, moderated by H. W. Magoun, M.D., College of Medicine, University of California, Los

Angeles, at which these papers will be presented:

*Psychic and Visceral Functions of Limbic Cortex and Rhinencephalon*, Paul D. MacLean, M.D., Yale University School of Medicine, New Haven.

*Stress Mechanisms of Cephalic Brain Stem*, Dr. Magoun.

*Bulbular Regulation of Cardiovascular Activity*, S. C. Wang, M.D., College of Physicians and Surgeons, Columbia University, New York.

*Central Action of Anti-Hypertensive Drugs*, Jurg A. Schneider, M.D., Ciba Pharmaceutical Products, Inc., Summit, N. J.

Admission to the meeting will be by invitation only. Additional information may be obtained from the Medical Division, American Heart Association, 44 East 23 Street, New York 10.

Proceedings of the 1954 Council for High Blood Pressure Research Annual Meeting have now been published in book form and may be purchased from the Association at $2.50 per copy. For those who wish the proceedings of the 1952 and 1953 meetings, as well as last year's, a combined price of $4.00 has been set for the three volumes of proceedings. Inquiries and orders should be addressed to the AHA Medical Division.

## PLAN BROAD PROGRAM AT EUROPEAN CONGRESS

A wide range of topics in the cardiovascular field will come under discussion at the Second European Congress of Cardiology to be held in Stockholm, Sweden, September 10 to 14, 1956. According to a preliminary announcement of the Congress, the subjects to be covered through panel and round-table discussions include:

Etiology and Pathogenesis of Atherosclerosis; Isolated Atrial and Ventricular Septal Defects; Pulmonary Hypertension; Cardiac Output and its Regulation; Acquired Aortic Stenosis; Circulation in Hypothermia; Organic Peripheral Arterial Disease; Treatment of Essential Hypertension; Treatment of Paroxysmal Arrhythmias and other Ectopic Rhythms; Phonocardiography; Indications and Hazards of Heart Catheterization and Angiocardiography; Applicability of the Roentgenological Heart Volume Determination.

Although the Congress is intended primarily for members of European national cardiography societies, every effort will be made to accommodate physicians from outside of Europe interested in cardiology. Information on the Congress can be obtained by writing to Dr. Karl Erik Grewin, Secretary General, Second European Congress of Cardiology, Sodersjukhuset, Stockholm, Sweden.

*ERRATUM:* In the Program and Proceedings of the Ninth Annual Meeting of THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS, dates on pages 481, 487 and 506 should have read: Sunday, *November 6* and Monday, *November 7*.

## PROGRAM: SECOND ANNUAL MEETING OF THE COUNCIL ON COMMUNITY SERVICE AND EDUCATION

**MUNICIPAL AUDITORIUM, NEW ORLEANS, LOUISIANA, SUNDAY, OCTOBER 23, 1955**

HAROLD FEIL, M.D., CHAIRMAN, PROGRAM COMMITTEE

### Body Weight and Heart Disease

9:30 A.M. *Chairman: Herbert Pollack, M.D., Chairman Nutrition Committee*

Relationships of Body Weight to Heart Disease
*Herbert H. Marks, New York, N. Y.*

Metabolic Aspects of Obesity—Facts, Fallacies and Fables
*W. H. Sebrell, Jr., M.D., New York, N. Y.*

Discussants:

Modern Living Habits and Weight Control
*Grace A. Goldsmith, M.D., New Orleans, La.*

Public and Patient Education in a Weight Control Program
*C. Frances MacKinnon, Chapel Hill, N. C.*

How the Home and Housewife Can Contribute to a Weight Control Program.
*A. June Bricker, M.D., New York, N. Y.*

Summation—Nutrition and Heart Disease—Research Needs.
*Herbert Pollack, M.D., New York, N. Y.*

10:50 A.M. **Intermission.**

11.00 A.M. **Panel Discussion with Audience Participation.**
*Moderator: Martin G. Goldner, M.D., Brooklyn, N. Y.*

12:30 P.M. LUNCHEON SESSION—Cotillion Room, Jung Hotel.

The Community Service and Education Council—Where It Is and Where It Is Going
***Martin Cherkasky, M.D., Chairman, Council on Community Service and Education***

### Heart Disease and Rehabilitation

2:00 P.M. *Chairman: E. A. Irvin, M.D., Chairman Rehabilitation Committee*

Rehabilitation—An Extension of Modern Medicine
*Paul D. White, M.D., Boston, Mass.*

Discussants:

The Family Doctor Sets the Pace for the Cardiac
*John G. Smith, M.D., Rocky Mount, N. C.*

The Cardiologist and the Rehabilitation Team
*Herman K. Hellerstein, M.D., Cleveland, O.*

Industrial Medicine and Rehabilitation Opportunities
*F. Benedict Lanahan, M.D., Philadelphia, Pa.*

3:00 P.M. **Intermission.**

3:15 P.M. **Panel Discussion with Audience Participation**
*Moderator: E. A. Irvin, M.D., Dearborn, Michigan*

## COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE JOINT SESSION WITH COUNCIL ON COMMUNITY SERVICE AND EDUCATION

**MUNICIPAL AUDITORIUM, NEW ORLEANS, LOUISIANA**

**Monday, October 24, 1955** **9:00 A.M. to 12:30 P.M.**

### PREVENTION OF RHEUMATIC FEVER

**SPEAKERS:** *Lewis Wannamaker, M.D., Minneapolis, Minn.*
*Gene H. Stollerman, M.D., Chicago, Ill.*

**PANEL CHAIRMAN:** *Edward E. Fischel, M.D., New York, N. Y.*

### THE CARDIAC CHILD IN SCHOOL

**SPEAKERS:** *S. Gilbert Blount, M.D., Denver, Colo.*
*Anna Kalmanowitz, Boston, Mass.*

**PANEL CHAIRMAN:** *Bernard J. Walsh, M.D., Washington, D. C.*

# PROCEEDINGS

## of the

# 28th SCIENTIFIC SESSIONS

## of the AMERICAN HEART ASSOCIATION

## October 22–24, 1955

### Municipal Auditorium

### New Orleans, Louisiana

# PROGRAM COMMITTEE
# AMERICAN HEART ASSOCIATION
# 1954–1955

CLARENCE E. DE LA CHAPELLE, CHAIRMAN, *New York*
GEORGE E. BURCH, CO-CHAIRMAN, *New Orleans*

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THOMAS FINDLEY, *Augusta*
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GORDON MOE, *Syracuse*
H. J. SMITH,† *Arlington*
BERNARD J. WALSH, *Washington, D. C.*

† ***Deceased***

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MAURICE SOKOLOW, *San Francisco*

## COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

THOMAS FINDLEY, CHAIRMAN, *Augusta*
MEYER FRIEDMAN, *San Francisco*
ARTHUR J. MERRILL, *Atlanta*

## COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

BERNARD J. WALSH, CHAIRMAN, *Washington, D. C.*
LEON DEVEL, *Grand Rapids*
JESSE E. EDWARDS, *Rochester*
STANLEY GIBSON, *Chicago*
LOUIS E. MARTIN, *Los Angeles*

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SELECTION OF PAPERS: Abstracts submitted were evaluated by the Program Committee of the appropriate Sections or Councils of the American Heart Association. The final selections were made by the Program Committee of the Scientific Council on the recommendations of the Section Program Committees. In general, no author was included in the program more than once, nor were papers accepted if the author had submitted a proposal for a scientific exhibit on the same topic.

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# 28th SCIENTIFIC SESSIONS

# of the AMERICAN HEART ASSOCIATION

# October 22–24, 1955

## SATURDAY MORNING
## OCTOBER 22, 1955

## GENERAL SCIENTIFIC SESSION

### Clinical Cardiology and Cardiovascular Surgery

**Auditorium—9:00 A.M. to 12:30 P.M.**

***Chairman: Clarence E. de la Chappelle, New York, N.Y.***

***Co-Chairman: Robert L. King, Seattle, Wash.***

**Physiologic Changes Seen After the Use of $I^{131}$ in Chronic Pulmonary Insufficiency.** *W. F. Hamilton, B. Shannon Gallaher, W. F. Hamilton, Jr., Irene F. La Motte, Robert G. Ellison and Lois Ellison, Augusta, Ga.*

**Effect of Intravenous Administration of Potassium Chloride on Ectopic Rhythms, Ectopic Beats and A-V Conduction Disturbances.** *John C. Bettinger, Borys Surawicz, John W. Bryfogle, Benjamin H. Anderson, Jr. and Samuel Bellet, Philadelphia, Pa.*

**Left Heart Catheterization by Means of Transthoracic Left Atrial Puncture.** *Don L. Fisher and Maurice H. McCaffrey, Pittsburgh, Pa.*

**The Fluoroscopic Image Amplifier: Its Use for Cardiac Catheterization.** *Henry A. Zimmerman, Cleveland, O.*

**Analysis of Clinical Results From the Surgical Creation of Pulmonary Stenosis in Twenty Patients with a Large Communication Between the Left and Right Ventricles.** *J. Francis Dammann, Jr., and William H. Muller, Jr., Charlottesville, Va.*

**Present Clinical Evaluation of Fifty Patients With Mitral Commissurotomy Five or More Years Ago.** *O. Henry Janton, Philadelphia, Pa.*

**Arteriosclerotic Occlusive Disease of the Lower Extremities and Its Treatment by Homograft Replacement With Particular Reference to the By-Pass Procedure.** *Michael E. De Bakey, E. Stanley Crawford, Denton A. Cooley and Oscar Creech, Jr., Houston, Tex.*

**To Be Read If Time Permits**

**A Clinical Study of Complete Heart Block.** *James C. Wright, M. R. Hejtmancik and George R. Herrmann, Galveston, Tex.*

**Atrial Septal Defect: The Persistent Ostium Primum.** *S. Gilbert Blount, Jr., Oscar J. Balchum and Goffredo Gensini, Denver, Colo.*

### PANEL: Aneurysms of the Aorta

EDGAR V. ALLEN, *MODERATOR, Rochester, Minn.*
MICHAEL E. DE BAKEY, *Houston, Tex.*
CHARLES T. DOTTER, *Portland, Ore.*
JOHN W. KIRKLIN, *Rochester, Minn.*
HUGH MONTGOMERY, *Philadelphia, Pa.*
IRVING S. WRIGHT, *New York, N. Y.*

## SATURDAY AFTERNOON
## October 22, 1955

## GENERAL SCIENTIFIC SESSION

**Auditorium—2:00 P.M. to 3:00 P.M.**

***Chairman: Irvine H. Page, Cleveland, O.***

***Co-Chairman: E. Cowles Andrus, Baltimore, Md.***

**THE LEWIS A. CONNER MEMORIAL LECTURE: Primary Hypertension, *George A. Perera, New York, N. Y.***

**THE ALBERT LASKER AWARD: Presented to Carl J. Wiggers, Cleveland, Ohio, by Robert L. King, Seattle, Wash.**

# SIMULTANEOUS SCIENTIFIC SESSIONS

## Clinical Cardiology

**Auditorium—3:00 P.M. to 5:30 P.M.**

***Chairman: Thomas J. Dry, Rochester, Minn.***

***Co-Chairman: Robert W. Wilkins, Boston, Mass.***

**Cardiovascular Disease and Abnormal Tryptophan Metabolism Associated With Malignant Carcinoid.** *Albert Sjoerdsma, Thomas W. Mattingly and Sidney Udenfriend, Bethesda, Md.*

**Heart Pain: Mechanisms and Relief.** *Joseph T. Roberts, Buffalo, N. Y.*

**Clinical Use of Purified Streptokinase-Streptodornase (Varidase) Preparation in the Lysis of Intravascular "Clots."** *Mario Stefanini, Boston, Mass.*

**The Significance of Albuminuria In Congestive Heart Failure: A Clinicopathologic Study.** *Charles H. Scheifley, George A. Race, Otto P. Schumacher and Jesse E. Edwards, Rochester, Minn.*

**The Use of Intravenous Ganglionic Blocking Agents For Acute Pulmonary Edema.** *Myrvin H. Ellestad and William H. Olson, Long Beach, Calif.*

**Massive Intermittent Dose Method of Dicumarol Therapy in Myocardial Infarction.** *Herman K. Hellerstein, Eugene Vayda, William B. Newberry, Jr. and Harold Feil, Cleveland, O.*

**Angiocardiographic Diagnosis of the Cyanotic Types of Congenital Malformations of the Heart: An Eight Year Study of 218 Patients.** *B. M. Gasul, E. H. Fell, G. Hait, R. F. Dillon, C. J. Marienfeld and H. G. Bucheleres, Chicago, Ill.*

**To Be Read If Time Permits**

**Studies On Complete Atrio-Ventricular Dissociation With Special Reference to Stokes-Adams Syndrome.** *Herbert J. Kayden and Maria Stack, New York, N. Y.*

**A Simple Test for Detecting the Altered Cardiodynamics of Ventricular Failure or Mitral Stenosis.** *Richard Gorlin and John H. Knowles, Portsmouth, Va.*

## Basic Science and Circulation

**Stage—3:00 P.M. to 5:30 P.M.**

***Chairman: William F. Hamilton, Augusta, Ga.***

***Co-Chairman: Ludwig W. Eichna, New York, N.Y.***

**Studies of Stress in Experimental Myocardial Infarction.** *Thomas N. P. Johns and Byron J. Olson, Bethesda, Md.*

**Pathogenesis of Cardiovascular Abnormalities in Fetal Rats Following Transitory Maternal Pteroylglutamic Acid Deficiency.** *I. W. Monie, M. M. Nelson, C. D. C. Baird and H. M. Evans, Berkeley, Calif.*

**Malformations of the Heart and Great Vessels of Rats with Experimentally Induced Congenital Transposition Complexes.** *Marjorie H. Fox and Charles M. Goss, New Orleans, La.*

**Experimental Miliary Pulmonary Embolism.** *D. Laurent, R. Pick, L. N. Katz, G. Larrain, I. Levinson and H. Gold, Chicago, Ill.*

**Cardiac Anaphylaxis.** *Aaron Kellner, Mario Penna and Abraham I. Schweid, New York, N. Y.*

**Production of Cardiac Lesions in Rabbits by the Intravenous Administration of Meningococcal Endotoxin and Endotoxin in Association with the High Molecular Weight Polymer Liquoid.** *Richard L. Davis and Joel G. Brunson, Minneapolis, Minn.*

**The Mode of Action of Certain Ionic Anticoagulants.** *Erwin Sheppard and Irving S. Wright, New York, N. Y.*

**To Be Read If Time Permits**

**Plasma Factor Enhancing the Ability of Angiotonin to Cause Contraction of Rabbit Aortic Strips.** *O. M. Hellmer, Indianapolis, Ind.*

**Business Meeting**

## Cardiovascular Surgery

**Brown Room—3:00 P.M. to 5:30 P.M.**

***Chairman: Jere W. Lord, Jr., New York, N.Y.***

***Co-Chairman: George H. Humphreys, II., New York, N.Y.***

**The Diagnosis of Mitral Regurgitation by Cardioangiography.** *Philip W. Smith, Hugh A. Cregg and Karl P. Klassen, Marion, O.*

**The Surgical Treatment of Mitral Insufficiency By Total Circumferential Suture of the Mitral Ring (Mitral Purse-String).** *Robert P. Glover, J. C. Davila, R. G. Trout and N. Wood, Philadelphia, Pa.*

**Neurogenic Factors in Coronary Disease—Experimental Findings and Clinical Results of Selective Vagotomy.** *Sidney Scherlis and R. Adams Cowley, Baltimore, Md.*

**The Direct Surgical Repair of Congenital Intracardiac Defects.** *H. E. Warden, M. Cohen, R. A. Dewall, R. C. Read, J. B. Aust, R. L. Varco and C. W. Lillehei, Minneapolis, Minn.*

**Clinical and Hemodynamic Studies of Tricuspid Stenosis.** *Paul N. Yu, Dwight E. Harken, Frank W. Lovejoy, Jr., Robert E. Nye and Earle B. Mahoney, Rochester, N. Y.*

**Clinical Applications of Blood Vessel Replacement.** *Edward B. C. Keefer, Abel A. Lazzarini and Frank Glenn, New York, N. Y.*

**The Clinical Behavior and Operative Management of Popliteal Aneurysms.** *Jere W. Lord, Jr., New York, N. Y.*

**To Be Read If Time Permits**

**Resection of the Aortic Arch Using Vessel Couples.** *James D. Fryfogle and John T. Small, Detroit, Mich.*

**The Application of an Experimentally Induced Pulmonary Collateral Circulation to the Coronary Arteries by Cardiopneumonopexy.** *William E. Bloomer, John L. Kline, Romeo A. Vidone, Harold Stern, Martha Pitel, Averill A. Liebow, New Haven, Conn.*

**Business Meeting**

# SUNDAY MORNING
# October 23, 1955

## GENERAL SCIENTIFIC SESSION

### Clinical Cardiology, Circulation and Basic Science

**Auditorium—9:00 A.M. to 12:30 P.M.**

***Chairman: A. Wilbur Duryee, New York, N. Y.***
***Co-Chairman: Edgar V. Allen, Rochester, Minn.***

**Body Sodium and Water in Patients with Heart Disease.** *Saul J. Farber and Robert J. Soberman, New York, N. Y.*

**Treatment of the Low Salt Syndrome in Congestive Heart Failure Using Mercurial Diuretics.** *Albert L. Rubin and Warren S. Braveman, New York, N. Y.*

**Primary Pulmonary Arteriosclerosis.** *Don W. Chapman and Joseph Latson, Houston, Tex.*

**Relationship of Dyspnea to Acutely Induced Changes in the Pulmonary Vascular Pressures in Patients with and without Congestive Heart Failure.** *W. Hollander, W. E. Judson and R. W. Stone, Boston, Mass.*

**THE GEORGE E. BROWN MEMORIAL LECTURE:**

**Digital Rheoplethysmography,** ***George E. Burch, New Orleans, La.***

**The Effect of Exercise Upon the Oxygen Removal Ratio in Patients with Mitral Stenosis.** *Arthur Selzer, Carl L. Ebnother, Arthur O. Stone and Thomas V. Feichtmeir, San Francisco, Calif.*

**Sensitivity of the Respiratory Center in Patients with Cor Pulmonale.** *Alberto C. Taquini, Aquiles Roncoroni, Pedro Aramendia and Antonio Ross, Buenos Aires, Argentina.*

**Congenital Arteriovenous Fistulas in the Extremities: Analysis of 69 Cases.** *Gerald Coursley, John C. Ivins and Nelson W. Barker, Rochester, Minn.*

**To Be Read If Time Permits**

**The Induced Digital Vasoconstrictive Reflexes in Health and Disease.** *Travis Winsor, Wilbur A. Selle and Youssef Mawardi, Los Angeles, Calif.*

**Pathogenesis of the Lower Leg Syndrome: A Study of the Phlebodynamics of the Lower Extremity.** *H. D. McIntosh, S. C. Fell, A. T. Hornsby and J. V. Warren, Durham, N. C.*

# SUNDAY AFTERNOON
# October 23, 1955

## SIMULTANEOUS SCIENTIFIC SESSIONS

### Clinical Cardiology

**Auditorium—2:00 P.M. to 5:30 P.M.**

***Chairman: Emmet B. Bay, Chicago, Ill.***
***Co-Chairman: William H. Bunn, Youngstown, O.***

**Mechanism of Experimental Coronary Shock.** *C. M. Agress, H. F. Glassner and H. I. Jacobs, Los Angeles, Calif.*

**Adrenal Insufficiency in Patients with Myocardial Infarction and Shock.** *Benjamin Manchester, Washington, D. C.*

**Hemodynamic Studies in Five Patients with Heart Block and Slow Ventricular Rates.** *David C. Levinson, Lewis Gunther, John P. Meehan, Jr., George C. Griffith and Raymon J. Spritzler, Los Angeles, Calif.*

**Effects of Sympathomimetic Drugs on Ventricular Rhythmicity and Atrioventricular Conduction During Stokes-Adams Attacks.** *Paul M. Zoll, Arthur J. Linenthal, William Gibson, Milton H. Paul and Leona R. Norman, Boston, Mass.*

**The Graphic Recognition of Predominant Mitral Stenosis or Insufficiency.** *O. M. Haring, H. Trace, C. Aravanis and A. A. Luisada, Chicago, Ill.*

**Cholecystectomy in Patients with Coronary Heart Disease.** *John R. Keys, Thomas J. Dry, Waltman Walters and Robert Gage, Rochester, Minn.*

**Hemodynamic Patterns in Congestive Heart**

**Failure.** *M. Irené Ferrer, Réjane M. Harvey, André Cournand and Dickinson W. Richards, New York, N. Y.*

**To Be Read If Time Permits**

**Hemodynamic, Vectorcardiographic and Electrocardiographic Observations in Right Bundle Branch Block.** *Eugene Braunwald, Ephraim Donoso, Samuel O. Sapin and Arthur Grishman, New York, N. Y.*

**The Total Duration of Ventricular Activation.** *Henry W. Blackburn, Jr., and Ernst Simonson, Minneapolis, Minn.*

## PANEL: Disturbances in Electrolyte Metabolism in Cardiac and Renal Diseases

JOHN P. MERRILL, *MODERATOR, Boston, Mass.*
ARTHUR J. MERRILL, *Atlanta, Ga.*
WILLIAM S. SCHWARTZ, *Boston, Mass.*

## Basic Science and Circulation

**Annex—2:00 P.M. to 5:30 P.M.**

***Chairman: Gordon Moe, Syracuse, N. Y.***
***Co-Chairman: Arthur J. Merrill, Atlanta, Ga.***

**A Depressor Reaction Caused by Stimulation of the Descending Aorta in Man.** *William P. Crowley, Jr., Joseph B. Grace, Irwin J. Fox and Earl H. Wood, Rochester, Minn.*

**Peripheral Venoconstriction in Human Congestive Heart Failure.** *J. Edwin Wood and Julius Litter, Boston, Mass.*

**Influence of an Oscillating Bed on Blood Flow and Oxygen Tension of Ischemic Toes.** *Carlos Forno, Philadelphia, Pa.*

**The Physical Work of the Digital Blood Vessels in Hypertension.** *Milton Mendlowitz, Albert D. Parets, Theodore Gold and Stanley R. Drachman. New York, N. Y.*

**The Multiphasic Nature of Blood Flow, Velocity and Vascular Volume in the Upper Extremity of Man.** *Edward D. Freis, Harold W. Schnaper, Lawrence S. Lilienfield, Ilse M. Wilson and Renato Kovach, Washington, D. C.*

**Some Determinants of Total Peripheral Resistance.** *Lysle H. Peterson, Philadelphia, Pa.*

**Bronchospirometric Determinations of Pulmonary Function in Dogs after Complete Unilateral Ligation of the Pulmonary Vein and Artery.** *William F. Kistner, J. Gerard Mudd and C. Rollins Hanlon, St. Louis, Mo.*

**Hemodynamic and Autonomic Effects of Arteriovenous Shunts.** *A. S. Dontas, Ann Arbor, Mich.*

**The Basic Oscillating Mechanism of Periodic Breathing in Cardiac Failure.** *Arthur C. Guyton, Jack W. Crowell and John Moore, University, Miss.*

**The Hemodynamic and Metabolic Interrelationships in the Activity of Epinephrine, Norepinephrine and the Thyroid Hormones.** *William R. Brewster, Jr., James P. Isaacs, Patricia F. Osgood and Thelma L. King, Boston, Mass.*

**A Miniature Pressure Transducer for Intravascular and Intracardiac Use.** *Baruch Bromberger-Barnea, Clarence A. Maaske and Ivan Greenwood, Jr., Denver, Colo.*

**To Be Read If Time Permits**

**Coronary Artery Pressure and Contractile Strength of the Right Ventricle in Dogs.** *Peter F. Salisbury, Los Angeles, Calif.*

**Concerning the Geometric Shapes of Arteries and Arterioles: A Contribution to the Biophysics of Health, Disease, and Death.** *J. Vernon Jeffords and Melvin H. Knisely, Charleston, S. C.*

**Business Meeting**

## High Blood Pressure

**Brown Room—2:00 P.M. to 5:30 P.M.**

***Chairman: Thomas Findley, Augusta, Ga.***
***Co-Chairman: Eugene B. Ferris, Atlanta, Ga.***

**Salt and Water Balance in Experimental Hypertension.** *Sydney M. Friedman and Constance L. Friedman, Vancouver, Canada*

**Development of Hypertension and Cardiovascular-Renal Lesions During Adrenal Regeneration in the Rat.** *Floyd R. Skelton, Augusta, Ga.*

**Plasma Concentration of Epinephrine and Norepinephrine in Hypertension.** *William M. Manger, Jesse L. Bollman, Khalil G. Wakim, Joseph E. Berkson, Edward J. Baldes and Grace M. Roth, Rochester, Minn.*

**Decreased Urine Flow in Response to Benzodioxane in Patients With Pheochromocytoma.** *A. C. Corcoran, Harriet P. Dustan and Irvine H. Page, Cleveland, O.*

**Dynamics of Acute Failure of the Left Ventricle during Neurogenic Hypertension.** *J. L. Patterson, Jr. and H. G. Langford, Richmond, Va.*

**Neurogenic Factors in the Chronic Phase of Experimental Renal Hypertension in the Dog.** *P. Kezdi, Chicago, Ill.*

**A Review of 100 Successful Kidney Biopsies.** *Alvin E. Parrish and John S. Howe, Washington, D. C.*

**Observations on the Mode of Action of a Hypocholesteremic Agent.** *R. J. Jones, Oscar K. Reiss and E. L. Balter, Chicago, Ill.*

**The Effect of Two Metal Binding Agents on Plasma Cholesterol in Man.** *H. Mitchell Perry, Jr. and Henry A. Schroeder, St. Louis, Mo.*

**Effects of Reserpine and Chlorpromazine on Central Autonomic Vasomotor Mechanisms.** *C. G. Gunn, Jr., M. Jouvet and E. E. King, Los Angeles, Calif.*

**The Effect of Acute and Chronic Administration of Pentolinium Tartrate on the Blood Pressure and Cardiac Output in Hypertensive Patients.** *Josef R. Smith, Alberto Agrest and S. W. Hoobler, Ann Arbor, Mich.*

**To Be Read If Time Permits**

**The Acute and Chronic Effects of Pentolinium Tartrate on Water and Electrolyte Excretion in Hypertensive Patients.** *A. P. Crosley, Jr., G. G. Rowe, J. F. Brown, H. Tuchman, J. H. Huston and C. W. Crumpton, Madison, Wis.*

**Serum Lipoprotein Levels in Preclinical and in Advanced Coronary Artery Disease.** *Joseph T. Doyle, Louis S. De Lalla, A. Sandra Heslin and Ray K. Brown, Albany, N. Y.*

**The Clinical Picture of Aneurysm of the Abdominal Aorta.** *Charles D. Enselberg, New York, N. Y.*

**Mecamylamine in the Therapy of Hypertension.** *John H. Moyer, Edward Dennis, Ralph Ford and Coleman Caplovitz, Houston, Tex.*

**To Be Read If Time Permits**

**Observations on the Use of Radioactive Iodine in Paroxysmal Tachycardia.** *Herbert Gold and Eliot Corday, Los Angeles, Calif.*

**Chlorpromazine in Combination with Rauwolfia in the Treatment of Essential Hypertension.** *Harold B. Eiber, New York, N. Y.*

**Business Meeting, Scientific Council**

# MONDAY MORNING
# October 24, 1955

## GENERAL SCIENTIFIC SESSION

### Clinical Cardiology and High Blood Pressure

**Auditorium—9:00 A.M. to 12:30 P.M.**

***Chairman: George E. Burch, New Orleans, La.***

***Co-Chairman: E. Cowles Andrus, Baltimore, Md.***

**Rauwolfia Serpentina in Treatment of Coronary Artery Disease: Clinical Study of Anginal Syndrome with an Analysis of Methods for Accurate Evaluation of Therapy.** *B. I. Lewis, R. I. Lubin, L. E. January and J. B. Wild, Iowa City, Ia.*

**Use of Serum Transaminase in Detection of Myocardial Infarction in Uncertain Cases.** *Albert A. Kattus, Jr., Charles Semenson and Robert Watanabe, Los Angeles, Calif.*

**Sensory Nerve Ischemia as Part of the Shoulder-Hand Syndrome.** *H. G. Langford and P. D. Camp, Richmond, Va.*

**Experimental and Clinical Study of the Effect of Beta Sitosterol Administration On Intestinal Absorption of Dietary Cholesterol and the Plasma Cholesterol Content of Patients with Coronary Artery Disease.** *Meyer Friedman, Richard Homer and Sanford O. Byers, San Francisco, Calif.*

**The Physiologic Effects of Long-Term, High Dosage Estrogen Therapy on Adrenocortic, Testicular and Thyroid Function in Coronary Atherosclerosis.** *R. W. Robinson, N. Higano, W. D. Cohen, R. C. Sniffen and J. T. Sherer, Jr., Worcester, Mass.*

# MONDAY AFTERNOON
# October 24, 1955

## SIMULTANEOUS SCIENTIFIC SESSIONS

### Clinical Cardiology

**Auditorium—2:00 P.M. to 5:30 P.M.**

***Chairman: A. Carlton Ernstene, Cleveland, O.***

***Co-Chairman: John J. Sampson, San Francisco, Calif.***

**Heart in Dystrophia Myotonica.** *Charles Fisch, Indianapolis, Ind.*

**A Complication of Myocardial Infarction Resembling Idiopathic, Recurrent Benign Pericarditis.** *William Dressler, New York, N. Y.*

**Serologic Effects of Inflammatory Reaction in the Human Heart.** *Adolph J. Boltax and Edward E. Fischel, New York, N. Y.*

**Improved Method of Evaluating Circulatory Shunts by Use of Direct Recording Ear Oximeter.** *Curt A. Wiederhielm and Robert A. Bruce, Seattle, Wash.*

**An Electrocardiographic Pitfall—The Juvenile Pattern.** *R. H. Wasserburger and T. H. Lorenz, Madison, Wis.*

**Persistent Problems in the Diagnosis and Treatment of Bacterial Endocarditis.** *Charles K. Friedberg and Robert C. Taymor, New York, N. Y.*

**To Be Read If Time Permits**

**Current Indications for the Use of Anticoagulant Drugs in Cerebrovascular Disease.** *Robert G. Siekert and Clark H. Millikan, Rochester, Minn.*

**Coronary Blood Flow and Myocardial Metabolism in Valvular Heart Disease.** *John L. Read,*

*Reno R. Porter, Edward G. Bond and Sarah C. Bradford, Richmond, Va.*

**PANEL: The Role of Hemodynamic Data in Determining Operability**

S. Gilbert Blount, Jr., *MODERATOR, Denver, Colo.*
Richard Bing, *Birmingham, Ala.*
Richard Gorlin, *Portsmouth, Va.*
Harper Hellems, *Detroit, Mich.*
Earl Wood, *Rochester, Minn.*

**Business Meeting**

## Basic Science and Circulation

**Stage—2:00 P.M. to 5:30 P.M.**

***Chairman: Eugene A. Stead, Jr., Durham, N. C.***
***Co-Chairman: Carl J. Wiggers, Cleveland, O.***

**Effect of Anoxia on the Glutamic Oxalacetic Transaminase Content of the Myocardium of the Rat.** *Joseph M. Merrill, Janet Lemley-Stone and George R. Meneely, Nashville, Tenn.*

**Effect of Acetyl Strophanthidin Upon the Myocardial Metabolism and Cardiac Work of Normal Dogs and Dogs with Congestive Heart Failure.** *Robert E. Olson, George Roush and Maria M. L. Liang, Pittsburgh, Pa.*

**Anaerobic Tissue Metabolism in Various Types of Valvular Heart Disease.** *William E. Huckabee, Boston, Mass.*

**The Action of Iodoacetate on the Electric and Mechanical Activities of the Isolated Perfused Frog Heart.** *Morris Kleinfeld, Edward Stein and John Magin, New York, N. Y.*

**Effluographic Determination of Potassium Flux in Heart Muscle as Related in Time to Potential Changes (ECG) and Contraction Event.** *W. S. Wilde, J. M. O'Brien and I. Bay, New Orleans, La.*

**Relation of Potassium Ions in Extracellular Fluid to Ectopic Ventricular Arrhythmias Induced by K-Strophanthoside.** *A. Sidney Harris, John E. Firestone and Richard A. Liptak, New Orleans, La.*

**Electric Activity of the Sinus Node, Atrial Myocardium and Atrioventricular Node.** *D. Durrer, Amsterdam, Holland*

**Alternation of A-V Conduction Time.** *Richard Langendorf, Chicago, Ill.*

**The Image Tetrahedron in Man Determined by Reciprocal Stimulation of a Tridimensional Esophageal Electrode.** *Jacob I. Hirsch, Stanley A. Briller and Nathan Marchand, New York, N. Y.*

**Graphic Recording of Heart Sounds and Vibrations by a New Electronic Pick-up.** *Dale Groom and John A. Boone, Charleston, S. C.*

**A Test of the Einthoven Triangle and a Modification which Corrects for the Lateral Eccentricity of the Heart.** *C. V. Nelson and H. H. Hecht, Salt Lake City, Utah*

**To Be Read If Time Permits**

**Digitoxin and Uncoupling of Oxidative Phosphorylation.** *Santiago Grisolia, Kansas City, Kan.*

## Rheumatic Fever and Congenital Heart Disease

**Brown Room—2:00 P.M. to 3:00 P.M.**

**Business Meeting:** Council on Rheumatic Fever and Congenital Heart Disease. *Chairman: J. G. Fred Hiss.*

***Chairman: Bernard J. Walsh, Washington, D. C.***
***Co-Chairman: J. G. Fred Hiss, Syracuse, N. Y.***

**Brown Room—3:00 P.M. to 5:30 P.M.**

**Congenital Aortic Stenosis: Early Clinical Manifestations and the Late Development of the Classical Syndrome.** *Helen B. Taussig and Jesse Schessel, Baltimore, Md.*

**Congenital Aortic Stenosis.** *Daniel F. Downing, Philadelphia, Pa.*

**The Diagnosis of Anomalous Pulmonary Venous Connection at Cardiac Catheterization.** *H. J. C. Swan, Howard B. Burchell and Earl H. Wood, Rochester, Minn.*

**Results of Medical Management of Coarctation of Aorta Diagnosed In Infancy.** *Mary Allen Engle and Henry P. Goldberg, New York, N. Y.*

**Diagnosis and Treatment of Patent Ductus Arteriosus with Pulmonary Hypertension.** *F. Mason Sones, Cleveland, O.*

**Immunologic Evidence of Group A Streptococcal Infection in Patients Undergoing Mitral Commissurotomy.** *G. H. Stollerman, W. F. Lynch, M. A. Dolan, D. Young and J. B. Schwedel, Irvington-on-Hudson, N. Y.*

**Epidemiology of Rheumatic Fever in Miami, Florida.** *Milton S. Saslaw and Murray M. Streitfeld, Miami, Fla.*

**To Be Read If Time Permits**

**Electrocardiographic and Hemodynamic Correlation in Atrial Septal Defect.** *Weldon J. Walker, Thomas W. Mattingly, Byron E. Pollock, David B. Carmichael, Thomas W. Inmon and Ralph H. Forrester, Fort Sam Houston, Tex.*

**A Reappraisal of the Cardiac Physiopathology in Patients with Interventricular Septal Defect.** *James E. Odell, L. E. January, John W. Eckstein and James W. Culbertson, Iowa City, Ia.*

# ABSTRACTS OF PAPERS

GEORGE E. BROWN MEMORIAL LECTURE

## Digital Rheoplethysmography

*George E. Burch, New Orleans, La.*

The venous occlusion plethysmographic method for recording the mean rate of blood flow to a part is an old procedure which has received extensive use. Recently a sensitive method has been developed for measuring, continuously and simultaneously, throughout the pulse cycle, the time course of the volume, rate and acceleration of digital inflow, outflow and the difference between inflow and outflow in intact man. Basal and mean rates of digital inflow and outflow can also be measured by this method. These continuous curves (rheoplethysmogram) make it possible to time any event in digital inflow and outflow within the pulse cycle. These temporal, quantitative and qualitative factors may be integrated to provide information concerning the state of the peripheral circulation which was not available heretofore. The isolated quantitative data are interesting in themselves. For example, it has been found that the mean resting rate of blood flow per gram of digit is about equal to that per gram of brain, left ventricle and liver and about four times that per gram of whole body. The qualitative and quantitative variations in the rheoplethysmogram were found to vary considerably with normal physiologic states as well as with disease. The rheoplethysmogram shows, for example, peripheral circulatory alterations concerned with critical closing and opening phenomena. It also shows states of "tightness" and distensibility of the arterial and venous sides of the peripheral vascular system in association with changes in arterial blood pressure which contribute to the hemodynamic and circulatory phenomena of aortic valvular insufficiency. Rheoplethysmographic studies in subjects with chronic congestive heart failure revealed evidence for increase in digital arteriolar and venous tone. Digital flow was low. Intravenous administration of hexamethonium immediately increased their rates of digital flow. Digital flow was extremely high when subjects were in hot and humid environment and almost zero when in a cool (12C.) atmosphere.

LEWIS A. CONNER MEMORIAL LECTURE

## Primary Hypertension

*George A. Perera, New York, N. Y.*

Doctor Conner was always keenly aware of the fact that ill persons place their confidence in a physician. Many of his actions conveyed the message that one must assume full heartily the responsibility imposed by this trust. The lecturer will illustrate this approach through the example of primary hypertension in a discussion of the physician's responsibility to himself, toward the illness and to his patient.

A position is taken that there is such a disease as primary hypertension, that it varies considerably in its course with either arterial or arteriolar emphasis, and that the accelerated phase is not just a quantitative change in tempo but rather the superimposition of a qualitatively different process. The position is taken that some persons have an inherited susceptibility to vascular alterations as the result of a metabolic derangement, with subsequent increasing participation of the kidneys.

Following a discussion of the natural history of primary hypertension, present day management of the patient is outlined. The pros and cons of supportive measures, diet, surgery and drugs are discussed. Particular emphasis is placed on those therapies which have an established effect and those which should be regarded as a continuing experiment. It is clear that in many patients means are available to relieve symptoms, to lower the blood pressure, to modify such fluctuations as congestive heart failure and retinopathy, and to prolong the life of some individuals in the accelerated phase of their illness. The physician's responsibility must include careful appraisal of the relative risks of these procedures and the possible effect on the patient as a whole.

**Abstracts are printed alphabetically according to the senior authors**

## Studies of Normal and Ectopic Atrial Activation

*J. A. Abildskov, T. G. Barnes and B. L. Hisey, Fort Bliss, Tex.*

Excitation, originating at the S-A node and several ectopic sites, was studied using molds of 5 normal human atriums. Spread of activation was represented by concentric arcs about the site of origin, and P loops and P waves in the standard and unipolar limb leads were derived using established principles of analysis for waves propagating on a surface.

Waves resulting from S-A node activation were derived by two methods, one of which assumed that

the limb electrodes are equidistant from all portions of the atriums, and another which considered the effect of actual distances between atriums and electrodes. P waves, derived by these methods were similar, indicating that the assumption of equidistance of limb electrodes is reasonably valid for normal atria. Waves derived from S-A node activation were similar to those in ECGs recorded shortly before the patients' death, supporting the validity of methods employed.

P loops and waves were derived from excitation originating at the two atrial appendages, the region of the inferior vena cava and the body of the left atrium on each model. Impulses from the left atrial appendage yielded P waves which were negative or diphasic and of low voltage in lead I, upright or diphasic in II and upright in III. The loops had a characteristic form with marked irregularity in the midportion. Activation, originating near the inferior vena cava, gave P waves of a distinctive form with an initial portion of low voltage. With excitation originating in the body of the left atrium near the A-V groove, negative waves in lead I and II and diphasic waves or waves with a terminal portion of low voltage in lead III resulted. P waves and loops from excitation, beginning in the right atrial appendage, were more nearly like those from normal activation than those derived from other ectopic sites.

**Mechanism of Experimental Coronary Shock**

*C. M. Agress, H. F. Glassner and H. I. Jacobs, Los Angeles, Calif.*

The primary purpose of this report is to present a working hypothesis for the mechanism of experimental coronary shock. This thesis is based on the past three years work and in particular a hemodynamic study in which the relationships between cardiac output, peripheral resistance and blood pressure in coronary shock and in dogs suffering severe myocardial damage without hypotension have been investigated.

The production of shock following coronary embolization of the closed-chest dog with plastic microspheres has previously been shown to be a critical function of the caliber of the coronary artery occluded. In those studies, protracted shocklike falls in blood pressure were produced consistently when microspheres of 325 $\mu$ in diameter were used. However, dogs injured by successive coronary embolization with microspheres of 450 $\mu$ or 190 $\mu$ in diameter did not go into shock, even when injured, until death occurred. The direct Fick method of cardiac output measurement, using manometric Van Slyke oxygen analyses, was employed in the current study. These studies show that the shocklike falls in blood pressure after coronary embolization with the critical size spheres were not due to extreme reductions in cardiac output. In a series of experiments in which dogs were embolized with spheres of 450 $\mu$ in diameter, reductions in cardiac output of up to 70 per cent from the control value occurred without the production of marked hypotension. In these experiments, the calculated total peripheral resistance rose as much as 300 per cent from the control value. On the other hand, dogs embolized with the critically sized microspheres showed an average fall of 30 per cent in mean arterial pressure and their cardiac outputs were found to be reduced by approximately 35 per cent from their control values. The calculated values for total peripheral resistance remained relatively constant.

These data suggest that occlusion of certain critical vessels in the dog heart invokes a mechanism, probably neurogenic, which, in some as yet undetermined manner, causes the inhibition of a compensatory rise in peripheral resistance, thus permitting shocklike falls in blood pressure to occur.

**The Effect of Choline-Theophyllinate in Angina Pectoris**

*C. Aravanis, Chicago, Ill.*

A study of the clinical effect of a choline-theophyllin compound was made in 64 clinical cases of angina pectoris. The patients were divided into 2 groups, 35 cases received three tablets daily (200 mg. of the vasodilator drug) and 28 cases received 3 identical placebo tablets. As the author did not know which of the 2 batches contained the drug, suggestive action was identical in both groups of cases.

Clinical data, the ECG, ballistocardiogram and results of a two-step exercise test were studied before treatment, and every 2 weeks after treatment began. This was continued for six months in one-third of the cases and for two months in the others.

The results with the drug were as follows: 2 cases (6 per cent) were negative, 5 cases (15 per cent) showed slight improvement, 11 cases (33 per cent) showed marked improvement and in 15 cases (46 per cent, all complaints disappeared. With the placebo 18 cases (73.5 per cent) showed no improvement and minimal improvement occurred in 10 cases (26.5 per cent).

It is concluded that a remarkable action of the drug took place. A correlation between the various laboratory data and the subjective improvement is made. The mechanism of action of the drug is discussed.

**A Ballistocardiographic Study of Mitral Valve Disease**

*Sidney R. Arbeit, Pierre Moret, Mortimer L. Schwartz and Robert Richmond, Jersey City, N. J.*

A study was undertaken in the hope of resolving the conflicting reports in the literature as to the

nature of the ballistocardiographic abnormalities found in mitral valvular disease. Direct body displacement, velocity and acceleration traces were taken because it was felt that some of the differences in findings reflected the restricted frequency responses of the individual methods reported or the limitations inherent in the function of motion studied.

A consistent, reproducible pattern that distinguished the various types of mitral disease was found only on the acceleration curve of the ballistocardiogram. These specific patterns are presented, the limitations of the method discussed and the reasons for the superiority of the acceleration ballistocardiogram in this application are given.

**Unsuspected Cases of Acute Myocardial Infarction**

*Samuel Baer, Philadelphia, Pa.*

For the past 20 years we have been engaged in a study of patients with acute myocardial infarction. The clinical course, ECG, laboratory and autopsy findings of more than 2,000 cases have been analyzed. Recently, we have been particularly impressed by that group of cases in which an unsuspected acute myocardial infarction has been found by accident.

We have been surprised at the frequency with which an unsuspected acute myocardial infarction has been demonstrated. These cases merit special emphasis. The acute infarction is not ushered in by pain of any sort but by one of its equivalents, or by dyspnea. Dizziness, unsteady gait, syncope or other neurologic abnormalities may be the only presenting symptoms. Some cases have been found when routine ECGs have been taken in postoperative patients, or patients with malignancy, biliary tract disease, uremia or pneumonia. Some of these cases of acute infarction are not apparent until serial ECGs are studied.

It is not generally realized that neuro-cerebral symptoms of apparently minor significance may be the only manifestation of acute myocardial infarction. The clinical features of these cases are discussed and representative protocols and ECGs are presented. The author feels that the widespread and routine use of the ECG will uncover more of these myocardial infarctions with bizarre symptomatology.

**Physiologic Evaluation of the Arterialization of the Coronary Sinus versus Implantation of the Internal Mammary Artery into the Left Ventricular Myocardium in Surgical Therapy of Occlusive Coronary Artery Disease**

*Alvin A. Bakst, New York, N. Y.*

These experiments elucidate alterations in the coronary circulation, following arterialization of the coronary sinus and implantation of the internal mammary artery into the left ventricle.

Retrograde coronary arterial blood flow, following circumflex ligation and oxygen content of this blood, were obtained in normal animals. The experiments were repeated in sinus arterialized animals of 2, 6, and 12 months duration and in animals having an internal mammary artery implantation for 6 months. All specimens were studied pathologically.

Normally, retrograde circumflex arterial blood flow is arterial, of small quantity and is a measure of intercoronary arterial collateral flow. In the sinus arterialized animals of 2-month duration, retrograde circumflex arterial flow is significantly increased, and the blood is deoxygenated. This suggests the retrograde perfusion of the myocardium. Following clamping of the graft, an increased intercoronary arterial collateral flow was demonstrated.

In the 6-month animals, retrograde myocardial perfusion by the arterialized coronary sinus cannot be demonstrated. However, an increase in the intercoronary arterial collateral flow persists. These findings were duplicated in the 12-month animals. All specimens revealed significant intimal proliferation within the major tributaries of the coronary sinus. Mortality studies reveal that after 1 year, arterialization of the coronary sinus no longer protects the heart against ventricular fibrillation, following coronary artery ligation.

In the series of animals in which the internal mammary artery had been implanted into the left ventricle for six months, the retrograde blood flow from the anterior descending artery was unaffected by clamping the implanted internal mammary artery, but was abolished by occlusion of the circumflex coronary artery. This demonstrated that the implanted internal mammary did not influence the collateral circulation of the anterior descending artery. All specimens revealed significant intimal proliferation of the implanted vessel throughout the intramyocardial tunnel. The mortality studies in this series demonstrated no protection to the heart against ventricular fibrillation.

**Clearance of Radioactive Iodine From the Extremities in Patients with Myocardial Infarction**

*F. K. Bauer, F. R. Mugler, Jr., V. W. Lieberman and J. P. Westergart, Los Angeles, Calif.*

It has been shown that determinations of the clearance of tracer amounts of radioisotopes do not give reproducible results when a needle is used, but that reproducible results can be obtained with a jet injector. It has also been shown that $Na^{24}$, $K^{42}$ and $I^{131}$ can be used interchangeably for clearance tests from local injection sites. Tracer doses of between .5 and 1 $\mu$c. $I^{131}$ in 1 ml. sterile saline were injected by Hypospray into the thighs of healthy control sub-

jects and 35 patients with recent myocardial infarction. The subjects studied were in the supine position. The solution penetrates deep into the muscle. A scintillation counter records the radioactivity. The time required for half of the radioactivity to disappear from the site of the injection is from 7 to 14 minutes, with a mean of 9 minutes. In patients with myocardial infarction, none of whom had congestive failure as evidenced by normal venous pressure and circulation time, the clearance times were greatly prolonged, sometimes for several weeks. Some of the patients were in shock and received noradrenalin; this prolonged the clearance, as could be expected.

It is believed that this delayed clearance of locally injected tracer amounts of radioisotopes indicates a diminution of the peripheral capillary bed. Whether this phenomenon is mediated through a reflex or a humoral mechanism, and whether it is due to diminished cardiac output is now under investigation.

**Effect of Molar Sodium Lactate in Increasing Cardiac Rhythmicity: Its Use in the Treatment of Slow Heart Rates, Stokes-Adams Syndrome and Episodes of Cardiac Arrest**

*Samuel Bellet, Fred Wasserman and Jerome I. Brody, Philadelphia, Pa.*

The effect of molar sodium lactate has been studied in 60 human subjects: these included patients with cardiac arrest (4 with Stokes-Adams seizures and 12 terminal cases), complete A-V heart block, partial A-V heart block, sinus bradycardia and other arrhythmias. In 3 of the 4 patients with Stokes-Adams disease, molar lactate restored ventricular beating on numerous occasions. In the 12 terminal cases, conspicuous improvement in the ECG was observed in most of the patients. The extent of its effect was related to administration within a critical period following cardiac arrest.

In patients with sinus bradycardia and partial and complete A-V heart block, the idioventricular rate was significantly increased. In one of these, where the control rate was 15 per minute with no obtainable blood pressure, the solution increased the ventricular rate to 60 per minute within a period of 4 minutes. After 5 hours of administration, the complete A-V heart block was restored to a partial A-V heart block.

The solution manifested a paucity of untoward effects even when administered in large doses and to patients with severe grades of myocardial damage. Except for transient extrasystoles in 6 cases, there was no evidence of the dangerous types of ectopic rhythm as are observed following epinephrine.

Studies performed on the dog, where complete A-V heart block and cardiac arrest were produced, yielded similar results.

It is felt that the administration of molar and one-half molar sodium lactate is an important addition to the therapy of cardiac arrest and slow ventricular rates. The exact mechanisms by which these changes occur are being investigated at the present time. Preliminary studies suggest that the solution acts by increasing the rhythmicity of the cardiac pacemaker.

**The Importance of the Electrocardiogram in Hyperpotassemia of Diabetic Acidosis**

*Michael Bernreiter, Kansas City, Mo.*

Hyperpotassemia is most commonly observed in patients with anuria since under normal conditions the kidneys will prevent abnormal accumulation of potassium (K). However in severe diabetic acidosis, before therapy is instituted the serum K level is elevated in most of the patients. Because the sodium (Na) content is lowered in diabetic acidosis the effect of hyperkalemia is enhanced. The concentrations of other ions influences the toxicity of K and therefore the serum K level itself does not necessarily give a true picture of the clinical state of the patient. The serum Na level may be practically normal during diabetic coma, but in view of the severe dehydration, these normal concentrations do not necessarily indicate a normal state of the electrolytes in the extracellular space. A therapeutic regime, therefore, based exclusively on the blood chemistry findings may be quite erroneous and detrimental to the patient. The ECG, however, reflects rather accurately the reaction of the heart muscle to the ionic environment. It is not a substitute for the measurement of the concentration of serum potassium, but it is a much more reliable diagnostic and therapeutic guide.

The correct and immediate treatment in diabetic acidosis is of the utmost importance since rapidly fatal potassium intoxication may occur. The greatest potential danger is in intravenous injection of potassium containing solutions. The most effective treatment of K intoxication is the prompt administration of glucose and insulin.

The usual sequence of ECG patterns, showing hyper- and hypopotassemia, is outlined.

**Effect of Intravenous Administration of Potassium Chloride on Ectopic Rhythms, Ectopic Beats and A-V Conduction Disturbances**

*John C. Bettinger, Borys Surawicz, John W. Bryfogle, Benjamin H. Anderson Jr. and Samuel Bellet, Philadelphia, Pa.*

Action of potassium on arrhythmias in patients receiving digitalis is compared with action of potassium on arrhythmias in patients not receiving digitalis.

The method consisted of administration of 6.0 to 60.0 mEq. of potassium (isotonic KCl) at a rate of 0.5 to 1.0 mEq. per minute, preceded by a control period during which 200 ml. of saline were infused

There were 59 patients, 2 with ventricular tachycardia, 16 with supraventricular tachycardia, 30 with sinus rhythm or atrial fibrillation and multiple ectopic beats and 11 with A-V conduction disturbances.

Ectopic rhythms and beats were abolished in 66 per cent and significantly depressed in 15 per cent of all cases. This effect occurred in 16 patients receiving digitalis (77 per cent) and in 22 patients not receiving digitalis (85 per cent). There was no significant difference in the effect of potassium on ventricular and supraventricular ectopic beats. There was no effect upon atrial fibrillation. The action of potassium in patients with low serum potassium levels was not significantly different than its action on ectopic beats with normal serum potassium values. When the effect of potassium was compared in patients with varying degrees of heart disease, there were again no significant differences. In the vast majority of the patients with ectopic beats the only significant effect of potassium consisted of disappearance of the ectopic beats. There was no effect on the sinus rate.

The serum potassium levels at the time of the maximal therapeutic effect did not exceed 6.8 mEq. per L. The duration of effect of potassium on arrhythmias varied from a few minutes to several weeks. Action of potassium on conduction disturbances was unexpected: complete A-V block was abolished in 3 cases and A-V conduction was improved in 4 cases. Intravenous administration of potassium proved to be a safe and effective method of treatment of arrhythmias regardless of presence or absence of hypopotassemia or digitalis medication.

### The Total Duration of Ventricular Activation

*Henry W. Blackburn, Jr. and Ernst Simonson, Minneapolis, Minn.*

Measurement of the QRS duration in any single lead is not accurate because it disregards the spatial QRS loop orientation. In this study, the total QRS duration was measured from the earliest to the latest instant of the QRS complex by using 3 bipolar orthogonal leads (horizontal X, vertical Y, sagittal Z), in order to correct for spatial orientation. Simultaneous events were recorded on a high speed (100 mm. per sec.), 2-channel machine (Mingograf) with excellent frequency and deflection time characteristics. The records were enlarged 10 times by projection. Longest duration from onset of QRS in any lead to the reference peak in the second channel was added to the longest duration from this peak to the end of the QRS complex in any lead to obtain total QRS duration. Positional variability was reduced by recording during relaxed breath-holding at the end of normal expiration. The minimal consistently measurable deflection from the "least slope" (Lepeschkin) was considered one half the width of the baseline, averaging 0.2 mm. in the original tracing. Measurement error was 2 msec. The QRS duration range in 115 healthy males age 20 to 50 was .0801 to .1309 seconds, mean .1010 seconds; 54 per cent of values fell above .10 seconds, 18 per cent above .11 and 3.5 per cent above .12 seconds. In 30 per cent of subjects, the earliest and latest deflections occurred in the sagittal Z lead alone. Comparison was made to the QRS duration recorded in single limb leads. Measurement of the variability of total QRS duration in different beats suggests that it might not be as stable as commonly considered. The correlation between total QRS duration and heart rate, body weight and age was determined. Application was made to QRS changes after exercise in normals and in cardiac patients.

### Acute Myocardial Failure During Rapid Rewarming Following Hypothermia in the Dog

*Emil Blair, A. Vernon Montgomery and Henry Swan, Denver, Colo.*

It is the general impression that the dog may be subjected to extreme levels of hypothermia and then rewarmed back to a normal physiologic status. The present report concerns the cardiovascular effects of hypothermia and of rapid rewarming.

Studies was set up to permit observations of the work of the heart, including cardiac output, resistance to blood flow and related ventilation. Following a period of 30 minutes to allow for a steady state, control normothermic runs were done, after which the animal was immersed in an ice bath and cooled to a rectal temperature of 30 C. Repeat studies were made at this point and again 1 hour later, after a steady hypothermic state at that temperature had been attained. The animal was then placed in a bath of water 42 to 45 C. and rapidly rewarmed to control temperature levels. Studies were done at this time and at regular intervals up to 3 hours post rewarming.

In the cooled state, there was a general decline in cardiovascular-pulmonary activity commensurate with lowered body metabolism, including diminished ventilation, lowered oxygen consumption, decreased blood flow with elevated vascular resistance, moderate acidosis, low blood pressure, slow heart, low cardiac output, reduced ventricular work, but unchanged A-V oxygen difference.

Following rapid rewarming the animal developed circulatory collapse with hypotension, hyperventilation and increased peripheral vascular resistance. The most significant physiologic interpretation at this time was a combination of observations, suggesting acute heart failure of the low output type. The failure resulted in death in one-third of the animals. Data suggest that the mechanisms for the failure lie in derangements of the myocardium itself.

**Clinical Hypothermia: Cardiovascular Effects Including Study of Total Circulatory Occlusion in the Human**

*Emil Blair, Henry Swan and S. Gilbert Blount, Jr., Denver, Colo.*

The subjects in this study were patients with congenital or acquired heart lesions and were cooled to levels between 26 and 31 C. Direct brachial artery and venous pressures and ECG were recorded continuously during cooling, total circulatory occlusion and during rewarming. During cooling, the heart rate declined on an average of 50 per cent, the blood pressure 27 per cent, the latter occurring about 30 minutes before stabilization at the lowest temperature. In half of the patients, the venous pressure became elevated and in the other, lowered. Despite the fact that adequate blood pressure was maintained throughout, it could not be obtained by auscultation when the temperature reached 30 C.

The occlusion time varied from 3 to five and one-half minutes. Upon occlusion there was a rise in venous pressure, followed by a fall as the occlusion was maintained. The blood pressure dropped immediately to 0 to 30 mm. Hg, while the heart rate accelerated, then slowed again, particularly following coronary perfusion of neostigmine. Upon release, the venous pressure either rose or remained low, returning to control levels in about 20 to 30 minutes. The blood pressure in those patients 28 C. or higher showed an overshoot of considerable magnitude. In those below 28 C., there was no overshoot, but a gradual rise in the pressure to control levels over a period of 10 to 20 minutes. The peak of the overshoot was reached in 15 seconds, considerably longer than that following release of a Valsalva during normothermia. The ECG during cooling showed atrial fibrillation and wandering pacemaker. During the occlusion, there were frequent premature ventricular systoles. Upon release and rewarming, the heart returned to normal sinus rhythm.

During cooling there was a transient increase in stroke volume early and then again just before stabilization at the lowest temperature, after which the cardiac output remained reduced. These changes appear to be reflex in character. The cardiovascular reflexes and venomotor tone during the hypothermic state, while somewhat slowed, appear to be adequately functioning.

**Left Heart Catherization in Selection of Patients for Surgical Procedures Upon the Mitral and/or Aortic Valve**

*William S. Blakemore, Truman G. Schnabel, Jr., Peter T. Kuo and Stephen B. Langfeld, Philadelphia, Pa.*

A new technic of left heart catheterization was utilized to simultaneously measure pressures on each side of the mitral or aortic valves in 21 patients with severe rheumatic heart disease. This procedure aids in selecting patients, suitable for a cardiac operation.

A 20 cm. no. 18 thin walled needle was inserted paravertebrally into the left atrium. Two small polyvinyl catheters were passed into the left atrium and one was manipulated into the left ventricle in all but 4 patients. A third catheter was passed into the ascending aorta via a no. 19 needle, inserted percutaneously into the left femoral artery. Pulse curves, ECGs and phonocardiograms were simultaneously recorded. The size of the stenotic valvular opening was estimated from the pressure gradient across the valve and any significant degree of mitral insufficiency was diagnosed from simultaneous left atrial and ventricular pressure curves. These data when combined with estimates of cardiac output permit more accurate calculation of cardiac work and valvular orifice size than has been previously possible.

These studies provided a definitive diagnosis when other preoperative diagnostic procedures had failed. Five patients had aortic valvular disease and 9 patients also had mitral valvular disease. Two patients with aortic valvular disease had recurrence of their symptoms 2 years following aortic commissurotomy. Six patients had mitral valvular disease only. Another patient with severe cardiac failure was found to have no valvular disease, although the left atrial and left ventricular diastolic pressures were elevated. In addition to their diagnostic value, the data permit better understanding of some of the mechanisms involved in the production of heart sounds and the hemodynamic changes resulting from alterations in cardiac rate, cardiac output and ventricular filling time. One fatality occurred among the 21 patients.

**Clinical Use of Phenindione: Five Years' Experience**

*Ancel Blaustein, New York, N. Y.*

This study comprises treatment with phenindione of 973 cases, including the study of dosage, uniformity of action, resistance, incidence of prothrombin escape, toxic manifestations, counter effect of Vitamin $K_1$ emulsion, and ambulatory therapy in 2 cases over a 3 year period.

The dosage schedule is 300 mg. the first day, 200 mg. the second and 100 mg. the third, similar to that commonly used with dicumarol. The maintenance dose varies from 25 mg. to 125 mg. per day. It may take from 7 to 10 days to establish the individual maintenance dose, but once established, consistent results are obtained. The smaller doses of 25 to 50 mg. per day were needed in cases of mitral stenosis with atrial fibrillation.

In 67.6 per cent of the patients the desired pro-

thrombin level was reached by 36 hours and by 48 hours it had increased to 90.3 per cent. Once the desired level was reached, it fluctuated little if the daily dose was divided in two. In the series of 973 cases, 16 cases or 1.6 per cent were resistant to therapy. Ten of these showed initial resistance and 6, delayed resistance.

In this series the incidence of prothrombin escape was 15 per cent and the average duration was 2 days. The mean correctional dose was 500 mg. phenindione. Of these patients, 98 per cent were women, who stopped therapy during the menses; the other 2 per cent were patients who discontinued therapy to have teeth extracted.

**The Application of an Experimentally Induced Pulmonary Collateral Circulation to the Coronary Arteries by Cardiopneumonopexy**

*William E. Bloomer, John L. Kline, Romeo A. Vidone, Harold Stern, Martha Pitel and Averill A. Liebow, New Haven, Conn.*

An attempt was made to apply the enormous blood supply to the lung from the aorta, as collateral circulation to the heart. This blood supply is induced via expanded bronchial arteries, after interruption of the pulmonary arterial inflow. In contrast with simple pneumonopexy as applied by Lezius, this procedure should make fully saturated blood, impelled by the systemic aortic pressure, available to the heart.

By means of vinylite casts of the cardiac and pulmonary vessels, several types of anastomoses were demonstrated following the operative procedure in dogs: (1) transpleural anastomoses that join branches of the coronary and bronchial arteries; these may reach a diameter in excess of 1 mm. at approximately 1 year, (2) retrocardiac anastomoses that join greatly enlarged branches of the circumflex, usually the left atrial artery, to the expanded bronchial arterial plexus and (3) intercoronary anastomoses.

The hemodynamics in control and experimental animals were studied by angiography and by catheterization. By means of the latter, it was determined that after approximately 1 year following the cardiopneumonopexy, some 2 to 5 per cent of inflow into the coronary sinus is received from the collateral vessels. The total flow into the coronary sinus was measured by the nitrous oxide technic. The direction and volume of the collateral flow were measured in the anesthetized dog by introducing Evans blue dye at a point in the aorta just above the ostia of the collateral vessels and by measuring the dye concentration curves simultaneously at four points: (1) In the femoral artery, (2) in the coronary sinus, (3) in the right atrium and (4) in the carotid artery (proximal to the point of introduction of the dye, to control a possible back circulation).

**Observations Following Direct Closure of Atrial Septal Defects**

*S. Gilbert Blount, Jr., Goffredo Gensini, Henry Swan and Malcolm C. McCord, Denver, Colo.*

Direct closure of an ostium secundum type of atrial septal defect has been accomplished in 32 patients by an open heart technic utilizing hypothermia and circulatory occlusion. Deaths related to surgery occurred in 3 patients ages 28, 32, and 33 years. These deaths occurred on the fifth, eighth and twelfth postoperative days.

Post-operative physiologic studies have been carried out in 23 patients and indicate complete obliteration of the left-to-right blood flow at the atrial level in all but 4 patients. The residual postoperative shunt was attributable to anomalous pulmonary venous drainage to the right atrium observed at the time of surgery in 2 patients. One patient has been reoperated and complete closure of a residual small atrial communication accomplished. The clinical course of the remaining patient who demonstrated a persistent postoperative shunt suggests that a spontaneous closure of the remaining defect has occurred. The systolic pressure in the pulmonary artery which exceeded 35 mm. Hg preoperatively in 10 patients returned to normal levels in all but 3 instances where a minimal elevation persisted. The total pulmonary arterial resistance at the time of the postoperative studies was elevated above 300 dynes per second per $cm^{-5}$ in 7 patients.

Clinical evaluation, postoperatively, revealed marked diminution in the intensity of the systolic murmur in the left second intercostal space in all patients. Obliteration of the diastolic murmur in the left fourth intercostal space was observed in all instances where this murmur was present prior to surgery. Fluoroscopic examination revealed a decrease in heart size, in cardiac activity and in vascularity of the lung fields. There was a significant regression of the incomplete right bundle branch block pattern which was present preoperatively. A completely normal right precordial lead pattern evolved in 3 patients and a considerable decrease in the amplitude of the secondary R wave was observed in the remaining patients. This method is thus recommended as a safe, effective procedure in patients with atrial septal defects, who present indications for operative intervention.

**Atrial Septal Defect: The Persistent Ostium Primum**

*S. Gilbert Blount, Jr., Oscar J. Balchum and Goffredo Gensini, Denver, Colo.*

Recent developments in the surgical therapy of congenital heart disease include the closure of atrial septal defects by various technics. The method employed at this institution consists of suture closure

under direct vision, open-heart surgery. The more frequent centrally located *ostium secundum* type of defect usually offers little technical difficulty to complete closure. The situation unfortunately differs greatly in the presence of the *ostium primum* type of atrial septal defect. Thus prior to surgery it is of more than academic interest, in fact, imperative to anticipate the type of atrial septal defect that may be encountered.

Five patients with an *ostium primum* type of atrial septal defect were studied by clinical and laboratory methods and the diagnosis verified either at the time of open heart surgery and/or at autopsy. The atrioventricular valves formed the floor of the defect and revealed congenital deformities in 4 of the 5 patients. Mitral insufficiency was present as a result of this valvular deformity in these 4 patients. This resulted in a high pitched systolic murmur at the left lower sternal area and/or the apex, and left axis deviation and indications of left ventricular hypertrophy on the ECG. The deformity of the mitral valve is considered to be the basis for these variations from the typical findings found in the patient with an ostium secundum type of atrial septal defect and make the differential diagnosis of the persistent ostium primum possible under these circumstances.

**The Effect of Experimental Acute Coronary Narrowing and Occlusion on Stimulation of Intercoronary Collateral Anastomoses**

*Herrman L. Blumgart, Paul M. Zoll, Milton H. Paul and Leona R. Norman, Boston, Mass.*

After acute coronary artery occlusion, the fate of the myocardium depends largely on the rate and extent of development of compensatory intercoronary anastomoses. In our previous studies on the development of anastomoses in response to experimental marked narrowing in animals, evidence of early development of collateral circulation were seen within 2 days, but 12 or more days were generally necessary for the evolution of a rich anastomotic circulation. Acute complete occlusion, in contrast to narrowing, creates a dynamically different situation and with the resultant infarction, it seemed quite possible that necrosis might alter, or even interfere with the development of anastomotic vessels.

Acute ligation of the peripheral left circumflex artery was performed in domestic pigs and the coronary arteries were injected at varying intervals, thereafter, with the Schlesinger lead-agar mass. In 178 normal hearts, anastomoses were almost uniformly absent. The present study of 23 animals demonstrates conclusively that collateral channels between unoccluded coronary arteries and the occluded segment of another artery begin to develop after 2 days. They are not uniformly present, however, until after 17 days.

In 3 human hearts, similar observations could be made concerning the time necessary for the development of intercoronary collateral circulation. All 3 hearts, with no evidence of old occlusions or areas of marked coronary narrowing, showed acute occlusion of a coronary artery with slight, incompletely developed anastomoses distal to it. All 3 patients died of acute myocardial infarction and 1 patient had a cardiac rupture. The times between onset of acute cardiac symptoms (probable time of acute coronary artery occlusion) and death were 5, 11 and 24 days in these patients. These 3 observations suggest that the development of anastomoses after acute coronary artery occlusion in man is similar to that observed in our animal experiments.

The implications regarding cardiac rupture and the advisability of minimal activity, following acute myocardial infarction, is discussed in relation to the protective ability of the collaterals to limit necrosis and to permit recovery of the injured tissue.

**Serologic Effects of Inflammatory Reaction in the Human Heart**

*Adolph J. Boltax and Edward E. Fischel, New York, N. Y.*

Nonspecific tests which reflect inflammation are in common usage as measurements of the degree of inflammatory activity in diseases such as rheumatic fever. Traditional methods include temperature, white blood count, and erythrocyte sedimentation rate (ESR). An increase in serum complement has been described in noninfectious inflammatory reactions and used as a measure of inflammation in acute rheumatic fever. Renewed interest in the C-reactive protein (CRP) and other tests makes it desirable to evaluate the tests in a comparable manner.

In myocardial infarction an injury is sustained which is not usually accompanied by inflammatory reaction elsewhere. Its onset can frequently be timed with great accuracy. This permits a comparison of various tests under similar conditions. Serial determinations of serum complement (C′), C-reactive protein (CRP) and ESR were done in 59 patients with 61 episodes of acute myocardial infarction. During the initial 24 hours, serum complement and CRP became abnormal more rapidly than did the ESR. At 48 hours, all three tests showed an equally high frequency of positive reactions. During the recuperative period, the CRP test tended to become negative more rapidly, occasionally at times when ECG changes continued to occur. This phenomenon has also been observed in the rapid disappearance of the CRP during the course of rheumatic fever at times when clinical and other evidences of inflammation continue.

The comparison of the 3 tests studied reveals some individual variation, but on the whole the simplicity and reliability of a well-performed Westergren ESR seems to justify its continued popularity for clinical purposes. It is of interest, theoretically, that the

CRP and C′ tests which were initially studied in relation to infectious or immune phenomena are abnormal in a non-infectious condition such as myocardial infarction. The role of these and other acute phase substances in the process of inflammation remains to be elucidated.

**Protein, Lipids and Heparin of the Human Aortic Intima (Comparison of Normal and Atherosclerotic Areas)**

*Robert J. Boucek, Nancy L. Noble and Kung Y. T. Kao, Miami, Fla.*

The atherosclerotic lesion is well circumscribed, suggesting localized tissue changes. Such discrete lesions prompted a study of the protein, lipids and octylamine-precipitable sulfates, termed heparin, of these areas.

Fresh human aortas, representing both sexes and varying age groups, were obtained at autopsy for study. The normal intima is transparent and quite thin, the early plaque is thick and opalescent and the plaque is characteristically golden-yellow. The isolated intima was frozen, pulverized, homogenized and separated into a saline-soluble and -insoluble fraction. Total protein, 19-amino acids, phospholipids, total and choline-containing, total and esterified cholesterol, total fatty acids and sulfates and octylamine-precipitable sulfates were determined. Total lipids and neutral fat were calculated from the lipid data. From the amino acid characteristics of the saline-soluble fraction, its identification as the ground substance appears likely, while the saline-insoluble fraction represents collagen and elastin.

The normal intima of the male has higher concentrations of cholesterol and total lipid and a lower concentration of heparin, than the tissue of the female. The phospholipids of both sexes consist entirely of choline-containing phospholipids. The intima of the premenopausal female has lower cholesterol, phospholipid and total lipid concentrations but greater heparin concentration than the intima of older females.

The early plaques of each sex contains a higher concentration of all the lipids, the male values exceeding the female values. A reduction in the concentration of heparin, in both sexes occurs in the early lesions. Plaques are richer in lipids and poorer in heparin than the younger lesions.

The concentration of the total protein of the various tissues remained unchanged, although differences in the concentrations of amino acids were observed in male and female tissue and in normal, early and plaque areas. The female tissue contains greater concentrations of arginine, lysine, proline, valine, leucine, phenylalanine and tyrosine. The male tissue is greater in its concentration of cystine and tryptophan. The plaque differs from the normal intima in its concentration of arginine, alanine and tryptophan.

The reported studies point out distinct sex and tissue differences among normal, early and late atherosclerotic lesions. Good correlation appears to exist between the concentrations of tissue lipids and heparin. The protein, amino acids and lipids are divided between the ground substance and the collagen and elastin. Heparin is found only in the saline-soluble fraction. The significance of the heparin, lipid and amino acid changes are discussed.

**Hemodynamic, Vectorcardiographic and Electrocardiographic Observations in Right Bundle Branch Block**

*Eugene Braunwald, Ephraim Donoso, Samuel O. Sapin and Arthur Grishman, New York, N. Y.*

The simultaneous registration of a ventricular pressure pulse and of an ECG permit measurement of the time interval between the onset of electric and mechanical ventricular activity. With significant right ventricular conduction disturbance, the interval between the onset of QRS and the onset of right ventricular contraction may be expected to be prolonged. This time interval, obtained by cardiac catheterization in 34 patients, was correlated with the spatial vectorcardiogram, employing the cube method and the ECG.

In 16 patients with clinical, electrocardiographic and vectorcardiographic evidence of right ventricular hypertrophy, the onset of right ventricular contraction followed the onset of QRS by normal intervals (0.045 to 0.075 second) indicating that significant right ventricular conduction disturbance did not exist.

In 12 patients with clinical evidence of right ventricular hypertrophy, the ECG showed complete or incomplete right bundle branch block. In 9 patients the vectorcardiogram revealed right ventricular hypertrophy without conduction disturbance, and the electric-mechanical interval was normal, indicating that no significant conduction disturbance was present. In the other 3 patients, however, the vectorcardiograms showed right ventricular hypertrophy with marked slowing of the terminal portion of the loop, suggesting the presence of conduction disturbance. The onset of right ventricular contraction followed the onset of QRS by abnormally long intervals, (.095 to 0.115 second) indicating that conduction disturbance did indeed exist in these 3 patients.

In 6 patients without heart disease whose ECGs showed incomplete or complete right bundle branch block, the vectorcardiograms presented terminal appendages, slowly inscribed, anteriorly and to the right. The electric-mechanic intervals were again prolonged, (0.095 to 0.110 second) confirming the presence of conduction disturbance.

These data indicate that the ECG pattern of right bundle branch block may or may not be associated with delayed right ventricular contraction and demonstrates the usefulness of the vectorcardiogram

in detecting right ventricular conduction disturbance.

**The Hemodynamic and Metabolic Interrelationships in the Activity of Epinephrine, Norepinephrine, and the Thyroid Hormones**

*William R. Brewster, Jr., James P. Isaacs, Patricia F. Osgood and Thelma L. King, Boston, Mass.*

Thirty-one dogs were made hyperthyroid by the feeding of 0.8 Gm. U.S.P. thyroid per Kg. of body weight per day for periods varying from 1 to 3 weeks. Twenty-seven euthyroid dogs were studied as controls. The serum protein-bound iodine concentrations of the euthyroid dogs averaged 1.7 μg. per cent. Following thyroid feeding, these serum protein bound iodine concentrations were found: in 7 to 10 days, 16.6 μg. per cent; in 11 to 15 days, 18.1 μg. per cent and in 18 to 22 days, 16.9 μg. per cent. Thyroid feeding produced the classical hemodynamic and calorigenic effects of hyperthyroidism, including significant increases in the heart rate, oxygen consumption, cardiac index and effective ventricular stroke work.

To differentiate between the effects of *l*-epinephrine and *l*-norepinephrine and those of the thyroid hormones, the reflex release of epinephrine was abolished in both euthyroid dogs and thyroid fed dogs by the use of a total epidural preganglionic sympathetic block. The total sympathetic block was produced by the epidural injection of a 0.45 per cent procaine HCl solution. The metabolic and hemodynamic effects of thyrotoxicosis could be abolished by preventing the reflex release of epinephrine and norepinephrine with a total sympathetic block. Studies done during a 1 to 4 hour period of total sympathetic block demonstrated that there was no significant difference in the oxygen consumption, cardiac indices, heart rates, average right or left atrial mean pressures, ventricular stroke work and arteriovenous oxygen differences of the thyroid fed dogs as contrasted to the euthyroid group of dogs.

All parameters of activity of *l*-epinephrine and *l*-norepinephrine were found to be increased by increased concentrations of the thyroid hormones. The infusion of either *l*-epinephrine or of *l*-norepinephrine into thyroid fed dogs with a total sympathetic block resulted in a rise in the oxygen consumption, heart rate, cardiac index and ventricular stroke work per unit of filling pressure that was significantly greater than that seen during their infusion in a comparable series of euthryroid dogs. The infusion of *l*-epinephrine or norepinephrine in euthyroid or thyroid fed animals resulted in equivalent inotropic, chronotropic or calorigenic effects, but there was a fundamental difference in the glycogenolytic effects of *l*-epinephrine and of *l*-norepinephrine, as reflected in the blood and serum concentrations of lactate, pyruvate and sugar. Whereas the infusion of *l*-epinephrine consistently resulted in a rise in the serum lactate and pyruvate and blood sugar, the infusion of *l*-norepinephrine, despite its equal calorigenic effect, produced a fall in the blood and serum concentrations of lactate, pyruvate and sugar. The normal values of serum lactate and pyruvate and of blood sugar observed in the thyroid fed animals in the control state suggest that *l*-norepinephrine is the predominant mediator of the physiologic effects of thyrotoxicosis, as far as the activity of the sympathetic nervous system is concerned.

It is concluded that there is a dynamic interrelationship between the thyroid hormones on the one hand and *l*-epinephrine and *l*-norepinephrine on the other. The physiologic effects of thyrotoxicosis are not the result of the isolated action of the thyroid hormones per se, but are due to the physiologic effects of *l*-epinephrine and of *l*-norepinephrine, as augmented by the thyroid hormones. The findings of other workers, as well as our own data, indicate that optimal concentrations of the adrenal cortical steroids are essential to demonstrate the interrelationship described above.

**The Spatial Ventricular Gradient**

*Stanley A. Briller and Michel Blondeau, New York, N. Y.*

By means of an originally designed electronic analogue computer, 52 determinations of the spatial ventricular gradient were made in 42 subjects. The isosceles tetrahedral reference frame was employed without correction for irregularities of the image surface. The vectorial QRST was recorded by electronic integration immediately after the vectorcardiograms in two planes. In addition to extensive electronic checks, accuracy was established by comparing instrumentally determined values for the spatial gradient and for the spatial vector of QRS with similar values determined planimetrically from conventional electrocardiograms.

The results obtained indicate (1) no significant difference between the range of values for the 10 normal subjects and for the 32 subjects with heart disease; (2) excellent agreement with the only other available series by Simonson and co-workers in which the spatial gradient and the spatial QRS vector were calculated in healthy persons; (3) in the normal group, the direction of the spatial ventricular gradient exhibited less variability than the mean direction of QRS; in the frontal plane the gradient invariably lay to the right of QRS as the direction of the latter varied from an angle $\alpha$ of 40 to $-45$ degrees and to the left for directions of QRS in excess of an angle $\alpha$ of 40 degrees; a similar anterior-posterior relationship of the 2 vectors was found in the horizontal plane; (4) in 5 cases of acute myocardial infarction studied serially, recovery from anterior wall necrosis was associated with clockwise rotation of the spatial gradient in the transverse and

frontal planes, whereas recovery from posterior wall disease was associated with progressive counterclockwise rotation of this vector in these planes; (5) absolute magnitudes and directions of the spatial ventricular gradient have little diagnostic usefulness, but intraindividual seriatim variations in the course of disease probably do, especially with instrumental means available for their rapid determination.

**Some Fundamental Considerations Concerning the Role of the Body's Electric Inhomogeneities in the Genesis of the Electrocardiogram**

*Daniel A. Brody and William E. Romans, Memphis, Tenn.*

Because of the present renascence of interest regarding the manner in which electric inhomogeneities affect the relationship between ECG deflections and the electromotive forces of the heart, we have undertaken a theoretic examination of the problem. Several basic biophysical principles evolving from this study appear to be of fundamental importance and should prove useful as a guide in devising and analyzing future experiments on human subjects. Although some of the conclusions reached seem rather paradoxical, we were able to demonstrate their validity experimentally in ECG models.

One such paradoxic conclusion concerns the short circuiting effect which presumably results from the relatively large electric conductivity of the intracardiac blood mass. Our findings indicate that this effect is exerted most strongly upon tangentially oriented electric doublets within the myocardium. Contrariwise, contributions to the ECG by normally oriented doublets are actually *enhanced* by the presence of the intracavitary blood mass. The relation between the two situations suggests that at least the QRS complex, as recorded by remote leads, may be due largely to normally oriented electromotive forces in the myocardium. These relationships may also explain in part the relatively low amplitude of the P wave.

In another phase of the study, the distortion produced in ideal lead fields by different conductivities of intracavitary blood, myocardium and surrounding lung tissue was determined and analyzed. An exact analysis was achieved for the heart, idealized as a spheric or ellipsoidal shell; an approximate result was obtained for a heart of somewhat irregular contour. These results indicate that certain lead connections, whose lead fields are ideal in the electrically homogeneous case, record the electromotive forces of the heart in at least a quasi-vectorial manner despite distortions introduced by electric inhomogeneity of the body.

**A Miniature Pressure Transducer for Intravascular and Intracardiac Use**

*Baruch Bromberger-Barnea, Clarence A. Maaske and Ivan Greenwood, Jr., Denver, Colo.*

A blood pressure transducer small enough to fit the leading end of an intracardiac catheter is presented. Its physical characteristics includes sensitivity, frequency response and linearity. The sensitivity is adequate for most biologic pressure applications. Frequency response of the unit exceeds that of the most commonly used gages at present, as determined by square wave impacts as well as by forced pressure cycling. The unit is based on a modified straingage principle and requires carrier wave amplification. Its small size enables it to be used on the leading tip of an intracardiac catheter, thereby obviating large effective masses with consequent wave distortion. The unit has so far been used on animals only. The pressure is recorded in situ and is electrically conducted through wires woven into the catheter wall to the recording instruments. The unit is a hollow cylinder so that blood samples can be withdrawn through it and the catheter in the usual manner.

The transducer has been implanted into large blood vessels of dogs (aorta and pulmonary artery). This enabled us to take abdominal aortic pressure in the unanesthetized animal. In these studies the unit is enclosed in a plastic bag filled with hypertonic solution and is sutured into the vessel wall without obstructing blood flow. These studies show remarkable pressure variations with movement of the abdominal contents. Records are presented comparing these with pressures recorded from the same location in anesthetized animals.

**Production of Cardiac Lesions in Rabbits by Cross Circulation and Temporary Arteriovenous Shunts**

*Joel G. Brunson and Richard L. Davis, Minneapolis, Minn.*

The internal carotid arteries and jugular veins of paired hybrid albino rabbits were connected, after administration of small amounts of heparin, by polyethylene catheters. Cross circulation was allowed to continue for a maximum period of 30 minutes after which the vessels were ligated. The animals were sacrificed 18 to 24 hours later.

Over 50 per cent of the hearts from these animals showed valvular and myocardial hemorrhages, areas of extensive muscle necrosis and mononuclear cellular reaction and coronary thrombi. Approximately 40 per cent showed, in addition, extensive deposits of fibrinoid material in the heart valves and walls of the coronary arteries. The valvular fibrinoid was often associated with the presence of many Anitschkow's cells and other large, mononuclear cells with basophilic cytoplasm.

Strikingly similar changes and an equal incidence of fibrinoid lesions of the valves and coronary arteries were observed also in the hearts of individual rabbits in which the internal carotid artery was connected

by polyethylene catheter to the jugular vein. Blood was allowed to circulate through this shunt for a maximum period of 30 minutes. The animals were sacrificed 24 hours later.

Morphologic changes in other organs were not observed in either group of animals. The incidence and extent of the cardiac changes and fibrinoid lesions were not altered appreciably in rabbits given an intravenous injection of meningococcal endotoxin prior to or after cross circulation or temporary arteriovenous shunt. Appropriate controls showed no cardiac changes of significance. Possible mechanisms concerned in the development of such lesions are discussed.

**Bilateral Incomplete Bundle Branch Block: A New Electrocardiographic Entity**

*J. Marion Bryant, Harvey J. Breit, William H. Wade and Ernest S. Shalaby, New York, N. Y.*

Incomplete right bundle branch block is common in normal persons although it can be the result of cardiac disease. Incomplete left bundle branch block is found predominantly with cardiac disease and may obscure or resemble myocardial infarction. Therefore, recognition of an ECG entity, consisting of both incomplete right and incomplete left bundle branch block is of investigative and clinical importance. Bilateral incomplete bundle branch block may be suspected from the routine ECG. It is probably not a rare finding in patients with heart disease. However, intracardiac studies with highly sensitive instruments and special technics are necessary to define this entity with certainty.

Limb, precordial, esophageal and right intracardiac leads were recorded simultaneously with Lead $V_2$ from a 70 year-old male with arteriosclerotic heart disease. A Sanborn Twin-Beam high-fidelity instrument was used. Deflections were measured to the nearest 0.002 second after 18 magnifications. Intracardiac leads were recorded at normal and lesser standardizations (the latter to allow registration of the whole complex on standard paper).

Small, initially negative, low-frequency ventricular deflections were recorded from *all* right ventricular cavity sites with normal standardization. These deflections indicated early activation of the interventricular septum from right to left. Together with a QRS interval of less than 0.12 second, they establish the diagnosis of incomplete left bundle branch block. With lesser degrees of standardization, these negative deflections were indistinct or invisible. Because of their disappearance or indistinct representation with (generally used) decreased standardizations it is probable that they were not always recognized in previous studies. A review of the published intracardiac ECGs affords some support for this suggestion.

In right ventricular cavity leads, the intrinsicoid deflections indicated that the interventricular septum was predominantly activated, although not initially, from its left side in an apex-to-base order. A secondary R-wave in $V_2$, in the absence of a simultaneous positive deflection in right ventricular cavity leads, established the diagnosis of incomplete right bundle branch block.

**Significance of Abnormal Phase II Response to Valsalva Maneuver in Cardiac Patients**

*Robert W. Burroughs and Robert A. Bruce, Seattle, Wash.*

Abnormal phase II pulse pressure response during the Valsalva maneuver has been described in patients with heart failure. To assess the validity and limitations of the response, arterial blood pressure was directly recorded during a standard Valsalva test in 19 control subjects and in 44 patients with heart disease. The latter were evaluated by the usual clinical criteria, an estimation of functional capacity (New York Heart Association), and, in 25 patients, by a standard exercise tolerance test. Maximal phase II responses (during latter half of 10 second expiratory strain with intraoral pressure of 40 mm. Hg) were $-47 \pm 20$ per cent below pre-Valsalva pulse pressure in 19 control subjects. Variance in two successive determinations in 15 subjects was 11 per cent. Only 5 of the 10 patients with significantly abnormal phase II responses had congestive heart failure. There was no correlation between phase II responses and functional capacity or exercise tolerance (expressed in terms of the physical fitness index). Both, false positive and negative results further limit the practical value of this method of assessing cardiac function which appears to be related to ability to obtain venous blockade by transient increments in intrathoracic pressures.

**Patent Ductus Arteriosus: Forty-one Cases Studied by Cineangiocardiography**

*Frank L. Campeti, Rochester, N. Y.*

Forty-one cases of patent ductus arteriosus have been studied by cinefluorographic angiocardiography, cinecardiometry and densitometry. The findings have been correlated with clinical findings.

With cinefluorographic angiocardiography, the angiocardiograms were recorded by the cinefluorocamera at 15 or 30 frames per second. The method of cinecardiometry consists of frame by frame tracings with measurement of several diameters of the right out flow tract and of the pulmonary artery (above and below the pulmonary valves and trunk, before the bifurcation and the right or left branches). By plotting the changing diameters, expressed in percentages, against time as the abscissa, specific curves are obtained indicating the activity of these structures and the deviation from the normal ones. With densitometry, the density (absorption) changes of the out-flow tract and the pulmonary artery (trunk and branches), corresponding to diameters

studied by cinecardiometry, have been recorded and traced on graph against time as the abscissa.

An unmistakable diastolic expansion of the pulmonary artery wave was found in all cases which showed the cineangiocardiographic evidence of shunting from aorta to the pulmonary artery (blanching sign). The usual decrease in density of the pulmonary artery, mainly near the bifurcation, as shown by densitometric curves is roughly inversely proportional to the positive diastolic wave of the cinecardiographic curves. During the left angiocardiogram, the densitometric curves of reopacification of the pulmonary artery from the opacified aortic blood correspond proportionally to the above described positive diastolic wave.

Three types of cinecardiometric curves were obtained. The first type (10 per cent of the cases) shows the diastolic reflux superimposed on the dicrotic wave, and represents protodiastolic shunting. In the second type (60 per cent of the cases) the wave begins in mid diastole and terminates with the onset of ventricular systole. The third type (30 per cent of the cases) is a telediastolic wave. An interesting, and so far unexplained observation in these cases, is a systolic narrowing of the pulmonary artery. The diastolic timing of the aorta-to-pulmonary artery shunt is believed to result from mechanical occlusion of the ductus, brought about by divergent paths taken by the pulmonary artery and aorta during systole. The clinical correlation is discussed.

**Primary Pulmonary Arteriosclerosis**

*Don W. Chapman and Joseph Latson, Houston, Tex.*

Primary pulmonary arteriosclerosis is defined by Brenner as idiopathic arteriosclerosis of the pulmonary arterial tree with marked right ventricular hypertrophy. It is considered a rare disease. We wish to report 9 cases studied, including symptomatology, physical findings, teleoroentogenograms, ECG tracings, cardiac catheterization and angiocardiographc observations.

The most prevalent symptom, early onset of progressive shortness of breath, was noted in all of the cases. In addition, hemoptysis, syncope, dizziness, pleuritic chest pain and terminal cyanosis were frequently encountered. Young asthenic appearing females predominated, occurring in 7 of our 9 cases. An enlarged right ventricle to physical examination was present in all of them. An accentuated second pulmonic sound was uniformly heard. Pulmonary systolic murmurs occurred in two-thirds and pulmonary diastolic murmurs in one-third of the patients. Clubbing of the nails was conspicuously absent as was suffusion of the conjunctivas.

Teleoroentgenograms routinely revealed evidence of right ventricular hypertrophy and a prominent undivided pulmonary arterial segment. In some, a pulmonary "hilar dance" was present. No evidence of left atrial hypertrophy was seen. ECG tracings showed right ventricular hypertrophy in 7 of 9 cases.

Right heart catheterization studies revealed marked elevation of right ventricular and pulmonary arterial pressures, normal "pulmonary capillary" pressures and decreased cardiac outputs. Arterial oxygen unsaturation was noted in the more severe ones.

The disease was noted to be progressive with right-sided cardiac decompensation predominating. Four of this series were autopsied and all revealed marked right ventricular hypertrophy, pulmonary arterial dilatation, pulmonary arteriosclerosis in the small arteries and arterioles with some malformation of the arterioles and capillaries. No evidence of systemic atherosclerosis was noted in any of them.

**A Simple Formula for Calculating QTc**

*G. C. Chiu and E. P. King, Indianapolis, Ind.*

The prolongation of the *Q-T* interval is of diagnostic value, especially in rheumatic carditis. Since the *Q-T* interval varies with the cycle length, the observed *Q-T* must be corrected for heart rate (*QTc*). For the calculation of *QTc*, the following formula is proposed:

$$QTc = \frac{2(Q\text{-}T)}{1 + (R\text{-}R)}$$

where *Q-T* is the measured interval in seconds between the beginning of the *Q* or *R* wave and the end of the *T* wave; and *R-R* is the interval in seconds between the *R* waves (cycle length). The upper limit for the normal value of *QTc* is 0.425 second.

Measurements obtained from normal subjects are analyzed. The proposed formula is compared with several others suggested in the literature. It agrees with Bazett's formula ($Q\text{-}T = K\sqrt{R\text{-}R}$) within the limits of normal variation, as shown by an analysis of variance components. Mathematic proof of this agreement, based on a Taylor's series expansion, is also presented.

The proposed formula appears to be particularly valuable for routine use because of its extreme simplicity. In contrast to other formulas, it does not require the calculation of square roots, cube roots or logarithms. It obviates the use of constants difficult to remember. The upper limit of the normal is the same, 0.425 second, using Bazett's formula, as the one recommended by the Criteria Committee of the New York Heart Association.

**The Cardiodecelerator Action of Veratrosine in Humans**

*Irwin R. Cohen and Edward Meilman, New Hyde Park, N. Y.*

Veratrosine, a secondary amine from veratrum viride, antagonizes the positive chronotropic, or cardioaccelerator, action of sympathomimetic amines

in laboratory animals. This effect is selective, the alkaloid showing no measurable influence upon myocardial contractility or blood pressure levels. Its applicability has been studied in 15 humans, both healthy and with various disease processes (hepatic cirrhosis, arteriosclerotic heart disease, lymphoma, hyperthyroidism and thrombophlebitis).

Subjects were studied in the fasting state and without other medications wherever possible. Control resting heart rate was obtained from ECG recordings. Veratrosine was then administered in various dosages intravenously through rubber tubing set up before the control period. Heart rate determinations were made every minute with the ECG. The blood pressure was recorded every 10 minutes.

Consistent slowing of the heart rate was observed in all subjects with an initial dose of 10 to 20 mg. Control heart rates ranged from 82 to 96 beats per minute, and fell to 58 to 66 beats per minute approximately 60 minutes after administration. Some cardiac deceleration was noted up to 150 minutes. Slowing of the heart rate averaged 22 beats per minute in the entire group, with significant slowing in each individual tested. The maximum dose, 40 mg. of Veratrosine, was needed over a 12-hour period to decrease the heart rate to about 60 beats per minute. The latter rate was taken as the desired end point, no attempt being made to determine the maximal decelerating potentialities of the drug at this time. There were no changes in the ECG. Side effects were infrequent. Two subjects complained of slight headache. One patient noticed nausea without vomiting. Studies are now in progress in patients manifesting various types of cardiac arrhythmias.

**Experimental Hydralazine Disease**

*Phillip Comens, St. Louis, Mo.*

Hydralazine hydrochloride (Apresoline), a vasodilator drug used in the treatment of arterial hypertension, was orally administered daily to normotensive dogs for several months in an attempt to reproduce the collagen-like syndrome found in man as a delayed toxic reaction to this drug.

The animals lost weight, developed muscular weakness and convulsions occurred in 3 of 7, resulting in death. Anemia, leukopenia, hyperglobulinemia and hypocholesterolemia were found in one or more. Electrophoretic patterns in 4 showed increased $\beta$, $\gamma$, and $\alpha_2$ globulins with decreased $\alpha_1$ fractions. Serums of treated and untreated dogs were incubated for 2 hours at 37 C. with leukocytes from normal human heparinized blood. L-E cell preparations on the human donors were negative. Using this modification of Carrera's technic, L-E cells were found in 5 surviving treated dogs after 1 to 2 months. Hematoxylin-staining bodies appeared in another, using dogs' cells and plasma. The abnormal cells disappeared on cessation of drug feeding and reappeared with reinstitution of therapy.

On the possibility that hydralazine, a metal binding agent, may produce the L-E phenomenon by removing some essential trace metal, 4 animals were fed the drug, 2 of these received, in addition, daily injections of manganese citrate and pantothenic acid. L-E cells developed only in the first pair. Of 2 groups of 10 chicks receiving hydralazine orally, manganese and pantothenic acid were given to one. Manifestations resembling perosis of manganese deficiency developed in two chicks receiving hydralazine alone; they have appeared sporadically in other chicks fed this drug.

**A Clinical Evaluation of the Standardized Clotting Time in the Control of Dicumarol Therapy**

*W. Ford Connell, Kingston, Ontario, Canada*

Forty patients on the wards of the Kingston General Hospital were given Dicumarol therapy for various clinical indications. Heparin was used to initiate treatment. Daily standard clotting times, as described by Mayer, and Quick one-stage prothrombin tests were performed. The patients were observed for a total of 719 treatment days.

In the entire series, there were 7 minor and 2 major hemorrhagic accidents. These all occurred at abnormally high clotting times, but 5 developed while prothrombin activity was in the "therapeutic" range. With progressive clotting time prolongation, the incidence of hemorrhage increased; no such correlation was noted with the prothrombin levels. Of the 27 cases of acute cardiac infarction in the series, 3 "poor risk" patients died; 1 developed severe gastro-intestinal hemorrhage with high clotting time and 2 had recurrent coronary occlusion, with too low clotting times. In all, the prothrombin test failed to give adequate warning of these events.

In this series, the standard clotting time has proven safer and more reliable than the Quick one-stage prothrombin test. Similar work is in progress with other oral anticoagulants. We believe this method is worthy of further controlled evaluation by experienced workers in this field.

**Influence of Gonadal Steroids on Serum Lipoproteins**

*Elmer E. Cooper, San Antonio, Tex.*

From the many clues afforded in clinical findings and lipoprotein spectrum analyses regarding relative susceptibilities of male and female to atherogenesis, the writer felt that a study of the influence of gonadal steroids on lipoprotein spectrums was indicated. The following conclusions seem justified from studies made in 30 cases.

(1) Estrogen administration to the male effects favorable changes in the lipoprotein spectrum from

atherogenic states to immune healthy patterns of premenopausal female.

(2) Castrated males have lipoprotein spectrums, similar to young premenopausal females.

(3) Prostatic carcinoma patients, with orchiectomy, estrogen therapy or both, have lipoprotein patterns far less atherogenic than normals of the same age group. Additional estrogen administered to the castrated male improves his atherogenic index.

(4) Estrogens in postmenopausal female with atherosclerosis secondary to diabetes or hypertension fail to improve lipoprotein spectrums.

(5) Estrogen lipoprotein changes in an atherosclerotic male was blocked by simultaneous androgen administration.

(6) Progesterone, compared to estrogen, has a lesser effect upon pituitary gonadotrophin blockage, and is found likewise, to have a lesser effect upon lipoproteins.

(7) Androgens have a highly unfavorable effect upon the lipoprotein spectrum in the eunuch, the eunichoid, the normal male and the normally immune premenopausal female. In each instance, the lipoprotein patterns were rendered definitely atherogenic.

(8) In a young atherosclerotic diabetic female, estrogens reduced her atherogenic lipoprotein pattern to normal while androgens rendered it highly unfavorable.

It has become apparent that gonadal steroids are very important in the development of atherosclerosis and that androgens very definitely affect the lipoprotein patterns unfavorably by placing the individual in a much greater atherogenic state. Estrogens influence atherosclerosis favorably by producing improved lipoprotein patterns. This effect however, is not due to estrogens "per se." Estrogens accomplish this only when they primarily depress androgen production via the pituitary gonadotrophin inhibition, or secondarily neutralize circulating androgen from the testes or adrenal gland origin.

**Decreased Urine Flow in Response to Benzodioxane in Patients with Pheochromocytoma**

*A. C. Corcoran, Harriet P. Dustan and Irvine H. Page, Cleveland, O.*

Infusions of adrenal medullary hormones in normal man tend to decrease Na and K outputs and to promote excretion of dilute urine at normal or increased rates of flow; urine flow decreases sharply when the infusions are withdrawn. We found that a similar sequence can be demonstrated in patients with functioning pheochromocytoma in whom adrenal medullary withdrawal is mimicked by giving benzodioxane.

This study is based on measurements of $C_{PAH}$, $C_{Mannitol}$, urine volume (V) and arterial pressure in 10 patients (these include 3 with pheochromocytoma); in 1 other with pheochromocytoma, the functions tested were $C_{PAH}$, $C_{Creatinine}$, urine volume (V), urinary osmolarity and outputs of Na and K. The 7 controls include 4 with essential hypertension, 1 with acute glomerulonephritis and 2 (1 with residual hypertension) whose pheochromocytoma had been removed. In these, benzodioxane elicited small increases of arterial pressure, irregular, small changes in $C_{PAH}$ and $C_{Mannitol}$; urine volume was unchanged in 1 and increased in 6. In contrast, in the 4 with functioning pheochromocytoma, benzodioxane caused moderate decreases in blood pressure, increases in $C_{PAH}$ in 2, and decreases in urine volume in all.

Decreased glomerular filtration (measured as $C_{Mannitol}$) may participate in the post-benzodioxane oliguria in 3 of these 4; however, in 1, $C_{Creatinine}$ was unchanged and sodium output and urinary osmolarity were both increased by benzodioxane. Thus, while the mechanism of this antidiuresis is not completely established, the regularity of its occurrence indicates that the response of urine flow to administration of benzodioxane may be a convenient confirmatory test in suspected pheochromocytoma.

**Congenital Arteriovenous Fistulas in the Extremities: Analysis of 69 Cases**

*Gerald Coursley, John C. Ivins and Nelson W. Barker, Rochester, Minn.*

Management of congenital arteriovenous fistulas in the extremities poses a difficult problem. Records of 69 patients with this condition, seen at the Mayo Clinic from 1935 to 1953, were studied in order to ascertain the efficacy of present management methods. The incidence according to age and sex, clinical features and contributory diagnostic aids were analyzed. The upper extremity was involved in 17 patients, the lower in 51, and 1 patient had involvement of both an upper and a lower extremity.

Twenty-eight of the 69 patients were treated medically, while the remaining 41 patients received surgical treatment or sclerosing injections. Prior to their initial visit at this clinic, 35 of the 69 patients underwent a total of 79 procedures. Of 26 patients who returned for subsequent examination, 20 underwent 40 separate procedures. Six patients were treated elsewhere and underwent a total of 10 procedures.

Two patients underwent major amputations following the initial examination at the clinic. There was an average follow-up period of 7.6 years for 53 of the patients. Of 13 patients with fistulas in the upper limbs, two were treated medically and the results were equivocal. Each of the remaining 11 patients underwent one or more surgical excisions of the fistulas. Among 5 patients who had localized fistulas there was only one recurrence. Of 7 patients who had more diffuse involvement, two subsequently

underwent major amputations at other institutions, 3 had recurrences and only 1 showed any degree of improvement.

Of the 53 patients whose condition was followed, 40 had fistulas in the lower limbs. Some patients were treated with indirect measures such as surgical treatment for varicose veins and sclerosing injections. Of this group, 1 patient with localized fistulas and 10 patients with diffuse involvement were not improved, 5 became worse and 2 patients showed some improvement.

After direct excision of 7 localized fistulas there were 3 good results, 1 fair result and 3 recurrences. Ligation of the arteriovenous communications was unsuccessful in 3 patients who had localized fistulas. Of 4 patients who had diffuse involvement, excision and ligation of the fistulas was followed by some improvement in 1 patient and poor results in 3 patients. Seven others with diffuse involvement were treated conservatively and only 1 patient showed any degree of improvement. One patient who had localized fistulas was continuing reasonably well without surgical treatment. Of 7 patients who underwent major amputations, 6 had diffuse involvement of the affected extremities.

### Experimentally Induced Atherosclerosis and Its Effect on Vascular Transplants

*Oscar Creech, Jr., George L. Jordan, Michael E. De Bakey, Robert C. Overton and Béla Halpert, Houston, Tex.*

The functional integrity of arterial homografts as well as the structural changes they undergo after transplantation both in experimental animals and in man are well known. There is, however, little or no information concerning the susceptibility of such vascular transplants to atherogenic factors in the host. Accordingly, this study is concerned with the effect of experimentally induced atherosclerosis on canine aortic transplants.

The experimental method for producing atherosclerosis consisted in rendering the animals hypothyroid by administration of $I^{131}$ and placing them on a diet resulting in chronic hypercholesterolemia. In addition to the control animals in which autografts were used, several groups of experiments were performed using aortic homografts preserved by freeze-drying and by refrigeration in balanced salt solution and tubes of plastic materials. These grafts were placed in the abdominal aorta to replace excised segments measuring 1.5 cm. The animals were sacrificed 6 to 18 months later and the heart and aorta with the graft were removed in continuity and fixed in formalin for about 48 hours. Gross and microscopic studies were then done using various methods of staining procedures.

These studies reveal a number of interesting observations. In animals with serum cholesterol levels in excess of 1,000 mg. per 100 cc., the host aorta and homografts were equally involved by atherosclerotic lesions. In those, however, with serum cholesterol levels less than 1,000 mg. per cc., there was only minimal or no involvement of the host aorta, whereas there was moderate to extensive involvement of the homograft. Autogenous aortic grafts behaved much like the host aorta. Only preliminary observations are available on grafts of plastic material. The significance of these studies as they relate to the metabolic atherogenic factor of hyperlipemia is discussed.

### The Acute and Chronic Effects of Pentolinium Tartrate on Water and Electrolyte Excretion in Hypertensive Patients

*A. P. Crosley, Jr., G. G. Rowe, J. F. Brown, H. Tuchman, J. H. Huston and C. W. Crumpton, Madison, Wis.*

Acute systemic hemodynamic studies in this laboratory have shown that the intravenous administration of 2.5 to 5 mg. of pentolinium tartrate to compensated hypertensive subjects was associated with a fall in mean arterial blood pressure due to a reduction in cardiac output with no significant change in total peripheral resistance. Simultaneous measurements of renal function have demonstrated statistically significant reductions in filtration fraction, renal oxygen consumption, as well as the urinary excretions of water, Na, KCl and buffer base. These changes were accompanied by a fall in urinary pH and a rise in urinary osmolarity. Systemically, these changes were reflected by a slight rise in whole blood pH, an increase in total $CO_2$ and a significant reduction in the hematocrit.

Results to date of chronic metabolic studies in hypertensive patients, receiving this agent by mouth, suggest that the acute findings may be of clinical significance.

### A Clinical Evaluation of Acetyl-Digitoxin

*R. B. Crouch, M. R. Hejtmancik, and G. R. Herrmann, Galveston, Tex.*

Acetyl-digitoxin has been derived from digitalis lanata in the hope of introducing a glycoside which would retain the favorable properties of digitoxin without the disadvantages of its slow dissipation and frequent side effects. We have made a clinical and laboratory study of its effects when given orally to 166 congestive heart failure patients of whom one-third had atrial fibrillation.

In 99 undigitalized patients, digitalization was achieved without difficulty by a single-dose method or over a period of several days, the average digitalizing dose being 1.84 mg. A single initial dose calculated on the basis of body surface area or body weight was well tolerated in 34 of 36 patients. Maintenance therapy was also effective, the daily requirement being 0.1 to 0.2 mg.

By stopping the drug in 7 fully digitalized patients with atrial fibrillation the rate of dissipation was determined and found to be slow but at least twice as rapid as that of digitoxin. Electrolyte studies on selected patients demonstrated conspicuous augmentation of excretion of water, Na and K. The therapeutic range was determined in 26 patients and was similar to that of other glycosides. Toxic effects were generally deliberately produced and were not serious in any case; these consisted solely of gastrointestinal symptoms in 25 of 32 patients, a higher proportion than with other digitalis preparations and has, therefore, an added safety advantage. It appears from these observations that acetyldigitoxin has merit as an effective long acting glycoside.

**The Electrolyte Excretion Pattern After Use of Various Digitalis Preparations**

*R. B. Crouch, B. de Pando and George R. Herrmann, Galveston, Tex.*

The importance of bed rest and low sodium diet have been accepted by physicians while the ease of administration and ever increasing number of powerful diuretics have caused physicians to place less emphasis upon the importance of digitalis in the treatment of congestive heart failure.

A clinical and laboratory study of the diuresis produced by digitalis has been made with particular emphasis upon the electrolyte excretion pattern produced. In addition a comparative study of the electrolyte excretion patterns of the various digitalis preparations has been made. Regardless of the type of digitalis preparation used, evidence of a 5 to 20-fold increase in the electrolyte excretion by digitalis was demonstrated. A comparison to the pattern of electrolyte excretion by mercurial diuretics was made and the relationship of the pattern of electrolytes excreted by digitalis in therapy of congestive heart failure is briefly discussed.

**The Effect of Fibrinolytic Activation on Survival and Cerebral Damage Following Various Periods of Circulatory Arrest**

*Jack W. Crowell and Edward E. Smith, University, Miss.*

Previous studies have shown that small blood clots form in the circulatory system when the blood flow is stopped. These small clots cause cerebral damage and/or death of the animals if the period of circulatory arrest is long enough.

If 75,000 to 150,000 units of streptokinase (Varidase) and a small amount of human plasma to activate the streptokinase are injected before the circulation is stopped, circulatory arrest of 10 to 15 minutes can be tolerated by the animals. Six dogs were given 75,000 units of streptokinase and 4 cc. of human plasma before being subjected to 10 minutes of circulatory arrest by fibrillating the heart. Then the heart was massaged and defibrillated. Four of the dogs were normal in from 1 to 5 days, another showed severe cerebral damage but is recovering, and one dog died of hemorrhage. Six dogs were given 150,000 units of streptokinase and 0.5 cc. human plasma and subjected to 15 minutes of circulatory arrest. Five of the dogs lived. Three of them showed very little cerebral damage, one absolutely none; two of the animals were sacrificed because of large necrotic ulcers that formed on the skin. Control dogs seldom survived circulatory arrest of more than 5 minutes duration.

The results presented offer evidence that blood clotting is the cause of death following temporary cessation of the circulation. Since several of the dogs have been normal on awakening from the anesthesia, it may be that small blood clots in the central nervous system is the factor causing transient cerebral damage in the remaining animals.

**A Depressor Reaction Caused by Forceful Intra-Arterial Injections in the Descending Aorta of Man**

*William P. Crowley, Jr., Joseph B. Grace, Irwin J. Fox and Earl H. Wood, Rochester, Minn.*

A depressor reaction has been encountered during the development of a method to measure thoracic aorta flow in man. In an attempt to facilitate uniform mixing of the indicator (T-1824) in the aorta, injections were made via an end-sealed (0.8 mm. O.D.) catheter with six radial holes (0.5 to 0.1 mm. in diameter) located near the tip.

At injection rates from 50 to 115 ml. per minute, the depressor reaction occurred in all 6 subjects and was absent when the injection rate was less than 20 ml. per minute. This reaction consisted of an increase in thoracic aorta flow and a fall in systemic pressure, followed by an increase in heart rate and respiration, associated with subjective sensations. These reactions began 4 to 9 seconds after the onset and persisted undiminished for the duration of the injection (15 to 75 seconds). Thoracic aorta flow increased, from a mean of 2.2 L. per minute shortly after the start of the injection, to 4.2 L. per minute at the height of the reaction. The range of increase was 50 to 140 per cent. Changes in both mean and diastolic arterial pressures were similar in aorta, femoral and radial arteries (mean 90 to 70 and diastolic 70 to 50 mm. Hg), while the average change in radial systolic pressure (136 to 123 mm. Hg) was less than in aorta and femoral systolic pressure (132 to 94 mm. Hg).

The reaction was obtained at every site of injection in the thoracic and abdominal aorta. It was not altered by omitting dye from the injectate, by substituting Ringer's solution for saline or by warming the injectate to body temperature. The reaction possibly represents a vasodilator response to hemo-

lyzed blood, produced by the high energy jet streams. It was not obtained when injections were carried out with an open-end catheter (0.05 mm. I.D.) under the same conditions.

**Observations on Circulation and Respiration after Bilateral Glossopharyngeal Nerve Section in Man**

*James H. Currens, Allan L. Friedlich, H. Thomas Ballantine, Jr. and Mandel E. Cohen, Boston, Mass.*

The glossopharyngeal (ninth cranial) nerves lies close to the vagus nerve and innervates the carotid sinus. When the opportunity arose of studying a patient with both nerves cut, observations were made on some aspects of circulation and respiration. The patient was studied after both glossopharyngeal nerves were cut intracranially for relief of pain. The pain was eventually demonstrated as resulting from carcinoma of the upper esophagus.

Circulatory studies were as follows: (1) blood pressure increased from 140/90 to 190/130, after nerve cutting but returned to 150/90, 2 hours later. (2) Carotid sinus stimulation by massage did not change the blood pressure or pulse rate; (3) protoveratrine (0.11 mg.) intravenously 4 times failed to demonstrate the usual fall (average change from 117/71 to 125/74, 15 minutes after protoveratrine); (4) in 20 normotensive controls, blood pressure fell after protoveratrine (0.11–0.12 mg.) intravenously (average change from 126/76 to 108/63); (5) finger pulsation increased after protoveratrine was administered intravenously (3.7 to 9.0 cm.) as did the finger skin temperature (11 F.); simultaneously there was little change in toe pulsation or skin temperature which are the expected changes after protoveratrine; (6) the expected fall in the cardiac index did not occur after protoveratrine intravenously (3.9 to 5.4 L. per minute); there was also the usual sensation of warmth in the face and neck and sweating over the head and face after protoveratrine.

Respiratory studies showed the usual effect of breathing carbon dioxide enriched air (rate increase from 14 to 18 per minute and respiratory volume from 5.9 to 11 L. per minute); there was failure of the characteristic gasp and acceleration in respiration after sodium cyanide administration up to 9.0 mg. intravenously.

These observations suggest that the glossopharyngeal nerves are important if not indispensable for the respiratory response to intravenous cyanide. It would seem that protoveratrine exerts a considerable portion of its effect upon the blood pressure through the glossopharyngeal nerves. The glossopharyngeal nerves are related to respiration and circulation in man.

**Analysis of Clinical Results from the Surgical Creation of Pulmonary Stenosis in Twenty Patients with a Large Communication between the Left and Right Ventricles**

*J. Francis Dammann, Jr. and William H. Muller, Jr., Charlottesville, Va.*

The basic concept involved in the surgical creation of pulmonary stenosis needs re-emphasis. In patients with a large communication between the great vessels or ventricles, the right and left ventricles function as one. A common systolic pressure is generated in both ventricles and consequently in both aorta and pulmonary artery. Therefore, the relative volume of blood flow to the lungs and to the body is dependent upon the peripheral vascular resistance. At birth, the resistance in the two circulations is essentially the same. Shortly after birth there is a progressive increase in lumen-size and decrease in wall-thickness of the small pulmonary artery with a consequent decrease in pulmonary resistance. As resistance falls, pulmonary blood flow increases. High output cardiac failure may result. In patients who survive cardiac failure, progressive sclerotic changes take place in the pulmonary arteries with a consequent rise in pulmonary vascular resistance and fall in pulmonary blood flow. These vascular changes may progress to the point where pulmonary resistance is actually higher than systemic resistance. If this occurs, cyanosis becomes prominent.

The surgical creation of pulmonary stenosis was devised to place an artificial resistance in the pulmonary vascular trunk, thereby increasing total pulmonary vascular resistance and decreasing total pulmonary blood flow. The presence of such an artificial resistance, in addition, removes the stimulus to progressive arteriolar thickening and permits the pulmonary bed to evolve in a normal fashion.

Since July 1951, 23 operations for the creation of pulmonary stenosis have been performed on 20 patients. The type of cardiac malformation present varied. Eight patients had a large ventricular defect with a common systolic pressure in both the right and left ventricles. Four patients had a medium sized ventricular defect with a significantly lower pressure in the right ventricle. Five patients had anatomic single ventricles. Two patients had an atrio-ventricularis communis, and one patient misdiagnosed as having a large ventricular defect, was found to have a large atrial defect with a congenitally malformed mitral valve. The common denominator in all was a communication between the right and left ventricles sufficiently large to raise the pulmonary systolic pressure and pulmonary blood flow. The creation of pulmonary stenosis was advised, in order to diminish the work of the heart by reducing the pulmonary blood flow or to prevent progressive pulmonary arteriolar changes.

Among the 20 patients there were 8 fatalities. Of these, 3 occurred before the chest was opened and two occurred because the pulmonary artery

for technical reasons, could not be narrowed sufficiently. One patient died of paroxysmal dyspnea 5 months postoperatively, one of cerebral thrombosis 3 days postoperatively and one of aspiration pneumonia 10 days postoperatively. Those patients who have survived have been, without exception, markedly benefited. Cardiac failure has disappeared, exercise tolerance has greatly increased and growth and development has followed a more normal course.

**Production of Cardiac Lesions in Rabbits by the Intravenous Administration of Meningococcal Endotoxin and Endotoxin in Association with the High Molecular Weight Polymer Liquoid**

*Richard L. Davis and Joel G. Brunson, Minneapolis, Minn.*

The effects of a single intravenous injection of meningococcal endotoxin in immature and mature rabbits were studied. Fifty per cent of the animals showed cardiac alterations consisting of myocardial and valvular hemorrhage, muscle necrosis and mononuclear cellular reaction and calcification of muscle fibers. Changes in the coronary arteries, consisting of intimal and medial edema and vacuolization and disruption of the endothelial lining, were also observed. In 10 per cent of the immature and 70 per cent of the mature rabbits, fibrinoid reaction was found beneath the endothelium of the coronary arteries and within the heart valves.

After 2 appropriately spaced injections of meningococcal endotoxin, 85 per cent of hearts from immature rabbits showed similar, but more extensive structural changes; fibrinoid lesions of the coronary arteries and heart valves were observed in 40 per cent. The valvular fibrinoid was often associated with the presence of many Anitschkow-like cells.

Similar cardiac changes occurred in rabbits given a single intravenous injection of meningococcal endotoxin in association with an intravenous injection of Liquoid. 70 per cent of the hearts showed coronary arterial and valvular fibrinoid lesions when the interval between the two injections was 18 hours. Other changes, consisting of the presence of renal glomerular capillary and splenic fibrinoid, hepatic thrombi and necrosis, pulmonary thrombi or emboli and, in those given endotoxin-Liquoid, bilateral adrenal hemorrhage and necrosis, were also observed.

The basic similarity between the lesions in each group is discussed. The morphologic features, distribution and chronologic development of the lesions, suggest an occlusive vascular phenomenon with resulting areas of ischemic necrosis. The morphologic and tinctorial features of the occluding material (fibrinoid) and the biologic activity of Liquoid, suggest that fibrinoid is derived from the circulating blood and that fibrinogen may be involved in its formation.

**Arteriosclerotic Occlusive Disease of the Lower Extremities and Its Treatment by Homograft Replacement with Particular Reference to the By-Pass Procedure**

*Michael E. De Bakey, E. Stanley Crawford, Denton A. Cooley and Oscar Creech, Jr., Houston, Tex.*

In the majority of patients with arteriosclerotic arterial insufficiency of the lower extremities, the occlusive process is located in the superficial femoral artery. Moreover, the occlusive lesion is often discrete and segmental in nature with the vessel being patent above and below it. As a consequence of this fortunate pathologic feature of the disease, it is usually possible to reestablish normal blood flow in the peripheral arterial bed. This may be accomplished by several methods including thrombo-endarterectomy, excision of the occluded segment with replacement by a graft and by means of by-passing the diseased area with a graft.

This presentation is concerned with our experience in 75 cases using the latter two methods of therapy, which have proved more effective. The procedure of excision and graft replacement is preferably employed in cases with relatively short occlusive lesions. In those with longer occlusions the by-pass procedure is considered more useful. It consists essentially in the addition of a large collateral vessel around the blocked area to those already present, but without disturbing them. Conceptually, therefore, it is based upon the natural response of the arterial tree to an occlusive process, namely the enlargement of collateral vessels around the obstruction. The procedure is accomplished by the anastomosis of an arterial homograft end-to-side to the patient's artery above and below the occluded segment through two small separate incisions which are connected by a tunnel in the subcutaneous tissues. Thus, in addition to restoring blood flow through the main arterial channel, this procedure has the advantage of producing minimal injury to lymphatics, veins and nerves and avoiding damage to collateral vessels.

Analysis of our experience with this method of therapy with follow-up studies ranging up to 2 years reveals highly gratifying results with few complications and no mortality. Excellent results with complete relief of symptoms have been obtained in over 90 per cent of the cases. Evidence of restoration of blood flow in the peripheral arterial bed is based upon pre- and postoperative studies, including arteriography and plethysmography.

**Are Aminophylline Suppositories Effective?**

*A. D. Dennison, Jr., Indianapolis, Ind.*

In spite of previous studies indicating the prompt effectiveness of theophylline preparations given rectally in solution form and a lesser effectiveness of rectal suppositories, approximately 6 to 7 million

suppositories of aminophylline are sold annually. This market amounts to almost $900,000 a year.

Great reliance is placed on theophylline suppositories in the management of cardiac asthma, Cheyne-Stokes periodic breathing and bronchial asthma. A comparative study was done on 10 patients determining over 150 theophylline blood levels after the administration of a theophylline preparation (monotheamin) to each patient by the intravenous route, by rectal retention enema or solution and by rectal suppositories. The theophylline blood levels were done by a more stringent modification of the Shack and Waxler method.

It was readily apparent that prompt effective theophylline blood levels were infrequently reached following the insertion of a 0.5 Gm. (7½ gr.) suppository. Within 15 minutes, significant blood levels were obtained and sustained, following the rectal retention enema or solution. Levels following the intravenous route were naturally immediately high and then fell off fairly rapidly. Because of low blood theophylline levels following the suppository insertion, the delay in obtaining significant elevations and indeed the infrequency of obtaining any reasonable therapeutic levels at all it is surprising that the medical profession employs aminophylline suppositories in such large quantities. It is equally surprising that the use of a rectal retention enema or solution which can be easily given and is therapeutically effective has not found wider acceptance. The clinical application of these findings was carried out in a large general hospital. These conclusions were also borne out in a more recent evaluation in private clinical practice.

**What is the Salvage Rate of Mitral Commissurotomy in Class 4 Cardiacs?**

*Clarence Denton and Houck E. Bolton, Philadelphia, Pa.*

The present study, based on a review of 61 patients with mitral valve disease who were totally incapacitated and at bed rest for a period of at least three months prior to surgery, reports the immediate and subsequent salvage rate of commissurotomy in this type of advanced disease.

Of the 61 patients, 12 (19.6 per cent) died immediately. Of the survivors, 9 died within 1 year, and 2 within 3 years after surgery. The cause of death was mainly congestive heart failure. However, mechanical issues may have contributed inasmuch as some degree of mitral insufficiency was created in 6 of these patients. Of the 38 patients presently living, 31 have been followed up for a period extending from 6 months to 3 years and 7, for 5 years.

Thirty-three of the patients have had a degree of functional improvement, warranting significant change in their cardiac classification. A single outstanding instance of an asymptomatic patient is reported. Evidence of improvement in cardiac murmurs, heart size and rhythm is in keeping with previous figures reported for more credible operative risks. Although mitral commissurotomy in class IV patients results in an operative mortality far in excess of the accepted ratio, according to our data it remains a therapeutic procedure capable of a remarkable alteration in the devolutionary pattern of the survivors.

**Retrograde Aortography: Its Application to Cardiovascular Diagnosis**

*Robert F. Dillon, H. G. Bucheleres, B. M. Gasul, E. H. Fell, C. J. Marienfeld and G. Hait, Chicago, Ill.*

Aortography, though widely recognized as a valuable diagnostic procedure, has had a surprisingly limited application to cardiovascular problems. We feel that aortography is a valuable adjunct to clinical appraisal which is often supplemented by such specialized technics as angiocardiography and cardiac catheterization. This report summarizes our experience obtained during aortography in 40 patients who presented congenital or acquired abnormalities of the heart and great vessels. There has been one fatality attributable to this procedure.

In infants, the retrograde injection of a 35 to 50 per cent concentration of contrast substance into the brachial artery has been most satisfactory. In older children and adults, the passage of a catheter into the optimal position and use of a more concentrated radio-opaque material has been necessary. Specifically, aortography is indicated in (1) differentiating a patent ductus arteriosus from a clinically atypical interventricular septal defect or an aortico-pulmonary fenestration; (2) defining the location and extent of a coarctation and the adequacy of the collateral circulation and (3), demonstrating a variety of congenital and acquired vascular abnormalities. The information obtained has important implications in the prognosis, medical management and feasibility of surgical intervention.

Selected case material is shown, depicting the aortographic appearance of patent ductus arteriosus, pre- and postductal coarctations, aortic septal defect and of a hypoplasia of the thoracic and abdominal aorta. Examples of congenital vascular anomalies include a cirsoid aneurysm of the face, and, to our knowledge, the first aortographic demonstration of anomalous vessels of the type found in intralobar pulmonary sequestration. The limitations and complications of retrograde aortography are summarized.

**Parenteral Reserpine in the Management of Hypertension**

*E. Grey Dimond and Fethi Gonlubol, Kansas City, Kan.*

Reserpine is generally considered a proper drug for mild, baseline effect in the management of hypertension. A small, daily oral dosage is the

standard method of administration. In an effort to gain a clearer idea of the hypotensive quality of the drug, we have administered it *parenterally* to 35 severe hypertensive patients.

In 20, the drug was given as a single *intravenous* preparation. The quantity varied from 40 to 100 μg. per Kg. In 6 of the 20, the pressure fell to normal and remained approximately 8 hours. In 6, the pressure fell materially but the diastolic pressure remained above 95 mm. Hg. In 8, no effect occurred, although the dose was steadily increased from 40 to 100 μg. per Kg. Side effects were primarily flushing and lethargy. However, 8 noted no side effect. Dextroamphetamine overcame the lethargy in most of the patients. In 3 patients in whom normal pressure resulted, the drug was given once daily for 10 days. Normotension, without postural hypotension and without serious side effects, resulted. Attempts to maintain the lowering of pressure by a similar or smaller oral dose were relatively unsuccessful, either because the pressure rose or because of severe side effects.

*Intramuscular* reserpine was next given in a similar dosage plan. This seemed equally effective. Nine patients were treated, 3 of these have been placed on daily, single injection therapy and have maintained marked falls in pressure without incapacitating lethargy or nausea. Dextroamphetamine and chlorpromazine are effective in overcoming the undesirable effects.

No serious or fatal reaction has occurred from 100 intravenous or intramuscular reserpine injections. The largest dose has been 7, the average 4 mg. Significant pressure lowering without tachyphylaxis occurs frequently. The parenteral drug, as compared to the oral preparation, is a much more effective hypotensive agent and produces fewer disturbing side effects. Daily intramuscular injections seem to be a very satisfactory means of treating severe hypertension.

**Hemodynamic and Autonomic Effects of Arteriovenous Shunts**

*A. S. Dontas, Ann Arbor, Mich.*

The immediate and delayed effects of terminoterminal, carotid-jugular or femoral-femoral arteriovenous shunts were studied in anesthetized, ventilated cats, immobilized by decamethonium. Simultaneous records were obtained through a multibeam oscilloscope of the carotid or femoral arterial pressure, right atrial pressure and action potentials from the contralateral carotid sinus and the efferent splanchnic nerves.

Opening of the shunt was associated with a slight drop of systolic and a marked decrease of diastolic pressure, no change in right atrial pressure or heart rate and usually a moderate increase in splanchnic activity associated with a decrease of pressoreceptor activity. Increase of right atrial pressure (thought to elicit the Bainbridge reflex), obtained by rapid intravenous injection of saline or glucose solutions, did not alter splanchnic activity. Occasionally, despite considerable hypotension, the carotid discharges were not decreased markedly, in which case splanchnic activity was not enhanced. The increase of splanchnic activity rarely lasted more than 10 to 20 seconds with shunts of this degree, despite the persistent arterial pressure change.

Closing of the shunt after 1 to 2 minutes was associated with only a momentary decrease or disappearance of splanchnic activity, coinciding with temporarily enhanced pressoreceptor discharge. When the shunt had been left open for periods exceeding 10 minutes, splanchnic inhibition was less pronounced. These observations suggest the rapid adaptation of the carotid-splanchnic system to long-lasting changes of pressures within the cardiovascular system.

**Congenital Aortic Stenosis**

*Daniel F. Downing, Philadelphia, Pa.*

Just as congenital obstruction to pulmonary flow may exist at the pulmonary valve or in the subvalvular region, so obstruction to systemic flow may exist at the aortic valve or in the subvalvular region.

Thirty patients with the lesion were studied. The physical findings were relatively uniform: a harsh systolic murmur and thrill in the second and third right interspaces, normal or decreased aortic second sound and a relatively normal systemic pulse pressure. All but 4 patients had symptoms of fatigue and shortness of breath; profuse perspiration was common. Syncope had occurred in only two. Two of the group died suddenly with no apparent precipitating cause. The majority showed the pattern of left ventricular hypertrophy on the ECG. The only relatively constant roentgen finding was dilatation of the ascending aorta.

Ten patients were operated upon. There was one operative death and one patient died following a cerebral embolus several weeks postoperatively. The results, to date, in the remaining patients have been satisfactory. An operation we believe is indicated in all patients with a significant obstruction.

**Serum Lipoprotein Levels in Preclinical and in Advanced Coronary Artery Disease**

*Joseph T. Doyle, Louis S. DeLalla, A. Sandra Heslin and Ray K. Brown, Albany, N. Y.*

Although the preclinical diagnosis is currently impossible, coronary artery disease is almost universally prevalent in middle aged American men. Pathognomonic alterations of the blood lipoproteins in coronary disease have not yet been described. The present study was undertaken to define the lipoprotein patterns in this vulnerable group of men as a prelude to extended serial observations.

From a carefully studied group of 2,100 office workers, 115 white men, 40 to 55 years old, were

selected. Forty men (group 1) were considered normal in respect to health record, familial susceptibility to vascular disease, current physical status and ECG response to standardized exercise. Twenty-nine men (group 2) were regarded as potential candidates for coronary disease because of factors such as obesity, elevated arterial blood pressure, diabetes mellitus or poor family vascular history; the electrocardiographic response to exercise was normal. Forty-six men (group 3) had authenticated coronary disease: 18 (group 3A) had angina pectoris and 28 (group 3B) had healed myocardial infarction.

Lipoprotein studies, including ultracentrifugal analysis and fractionation by Cohn's method 10, showed no significant differences in the mean values between groups 1, 2 and 3A, but highly significant differences from group 3B in total serum cholesterol, cholesterol and phospholipid levels of the $\beta$-lipoprotein and in $-S_{1.21}$ 10-52 lipoprotein class. Reciprocal changes in the $\alpha$-lipoproteins were not found. The nature and source of this increased lipid are under investigation.

**Evaluation of Cortisone and ACTH as Prophylactic and Therapeutic Agents in Postcardiotomy Syndrome in Patients with Rheumatic Heart Disease**

*David T. Dresdale, Charles B. Ripstein, Santiago V. Guzman and Murray A. Greene, New York, N. Y.*

The effects of cortisone and corticotropin (ACTH) as prophylactic and therapeutic agents in the postcardiotomy syndrome in patients with rheumatic heart disease is evaluated. This syndrome is referred to as the "postcardiotomy syndrome" (PCS) in patients with rheumatic heart disease rather than the "postcommissurotomy syndrome" because commissurotomy is not necessary for its development.

We observed 84 patients with rheumatic heart disease who underwent cardiotomy; of these 39 per cent developed this syndrome. For the prophylactic evaluation of cortisone, there were 26 patients (group 1) who served as controls and 58 patients (group 2) who received cortisone in dosage of 150 to 300 mg. daily for the first 2 postoperative weeks and then 75 to 150 mg. for the next 1 to 6 weeks. Eight (31 per cent) of the 26 patients in group 1 exhibited PCS during the initial 3 to 8 weeks after surgery. Four (7 per cent) of the 58 patients in group 2 developed the syndrome during a similar time period while on prophylactic cortisone. The syndrome subsided promptly in these four patients when the dose of cortisone was increased.

The incidence of the postcardiotomy syndrome (PCS) was similar in both groups, (31 per cent in group 1 and 29 per cent in group 2), after the initial postoperative period of 8 weeks when cortisone was discontinued. Cortisone in doses of 50 to 300 mg. daily was given to 21 patients during 65 episodes of PCS, usually because of various coexistent, distress complaints. In 62 episodes, there was a complete remission of the clinical findings within 24 to 36 hours. Two patients did not respond to 50 mg. daily, but remitted promptly on 200 mg. during later bouts.

A comparison is made of the efficacy of salicylates, Pyramidon, antibiotics and cortisone or ACTH in the treatment of the postcardiotomy syndrome. Cortisone or ACTH was superior to the other therapeutic agents which in general did not favorably affect the clinical manifestations of the syndrome. The frequency of the occurrence of the symptoms and laboratory findings and their response to cortisone and ACTH are discussed.

**Hemodynamic Effects of Cortisone in Patients with Rheumatic Heart Disease and Congestive Heart Failure**

*David T. Dresdale, Murray A. Greene and Santiago V. Guzman, New York, N. Y.*

Utilizing the technic of right heart catheterization, a study was made of the effects of prolonged cortisone therapy upon the cardiovascular hemodynamics in 6 patients with rheumatic heart disease, pulmonary congestion and right heart failure. Three patients had pure mitral stenosis whereas the other 3 had mitral stenosis with a considerable degree of insufficiency; 4 of the 6 had clinical evidence suggesting low-grade rheumatic activity. This study was undertaken because these types of patients, with or without evidence of rheumatic activity, showed improvement clinically in their cardiac status in most instances when given cortisone.

Physiologic studies were done at rest and after standard exercise during a control period and after the patients had been on cortisone in average doses of 75 to 200 mg., daily for 25 days to 9 weeks in 5 patients and 8 months in one patient. Blood volume determinations using T-1824 dye were obtained in five patients in both periods.

Clinically it was observed that 4 patients had some improvement in their symptoms and findings of cardiac decompensation. Three of these patients previously had evidence of rheumatic activity, the other one had none. There was no aggravation of the cardiac symptoms in any of the patients.

The physiologic studies did not show any increase in the severity of the already existing abnormal hemodynamics. In 2 patients who had evidence for rheumatic activity, one with pure mitral stenosis and the other with mitral stenosis and insufficiency, there was an improvement in the pulmonary vascular pressures. In one of these 2 patients there was a significant fall in the pulmonary capillary, pulmonary artery and right heart pressures, whereas in the other there was a fall in the pulmonary capillary

pressure at rest. There were no changes in the blood flows. Plasma volume decreased after cortisone administration in three of the patients, in one it did not change.

A correlation is made between the effects of cortisone as noted above and the known physiologic behavior of this steroid.

**A Complication of Myocardial Infarction Resembling Idiopathic, Recurrent Benign Pericarditis**

*William Dressler, New York, N. Y.*

A febrile complication was observed in 10 patients admitted to the Maimonides Hospital with recent myocardial infarction. Eight of the cases were observed within a period of 13 months. The syndrome did not fit any of the patterns listed in the text books as complications of myocardial infarction. Clinical and laboratory evidence pointed to pericarditis, pleurisy and pulmonary inflammation, the conditions occurring either singly, or, more often, in combination. There was a striking tendency for these symptoms to recur. One of the patients developed fever and pleuropericardial pain with evidence of pericarditis 2 weeks after a myocardial infarction. Six similar bouts followed within a period of 10 weeks, some of them associated with pleural effusion. Faure and Cazeilles reported a case in which, within a period of 8 weeks following acute myocardial infarction, 3 febrile bouts with pericardial and pleural effusion were observed. This complication is puzzling and, for lack of other etiology, often diagnosed as extension of myocardial infarction or pulmonary embolism. Yet neither the character of the pain nor serial ECG studies lent support to a diagnosis of extended myocardial infarction. Nor were there any signs of thrombophlebitis, hemorrhagic sputum or roentgenologic evidence of pulmonary infarction. The complication developed in patients treated with dicumarol as well as in those from whom anticoagulant treatment was withheld.

The clinical features greatly resemble those of recurrent idiopathic pericarditis or the postcommissurotomy syndrome. The etiology is unknown. A chance coincidence of myocardial infarction and idiopathic pericarditis is unlikely, because the incidence of the condition associated with myocardial infarction was greater than that of uncomplicated idiopathic pericarditis observed in the hospital during the same period of time. The prolonged febrile course and recurrent bouts of pain add greatly to the anxiety and nervous strain of the patient already aroused by the diagnosis of "coronary attack." Since the complication has so far proved to be of a benign nature, it is important that those called upon to treat myocardial infarction be familiar with the syndrome.

**Studies on the Control of Aldosterone Secretion**

*L. E. Duncan, F. C. Bartter and G. W. Liddle, Bethesda, Md.*

Although it has recently been established that aldosterone plays a role in normal sodium conservation and in the pathologic sodium retention of cardiac failure, nephrosis and cirrhosis, the factors controlling its production are poorly understood. To throw light on these factors, patients and normal subjects were studied under metabolic regimens; intake was constant, except when water and electrolytes were added or withheld according to the design of experiment. Some received cation exchange resin throughout the study. Aldosterone secretion was estimated quantitatively by urine assay and qualitatively from sodium uptake by resin; reciprocal changes in urinary sodium and potassium reflected aldosterone changes.

Three types of stimulus were shown to affect aldosterone output in normal subjects: ACTH, changes in dietary potassium and changes in body fluid volume. Each could be shown to act independently of the others; response to volume changes was quantitatively much greater than that to ACTH or potassium.

ACTH consistently produced roughly two-fold rises in aldosterone excretion; when it was stopped, aldosterone excretion fell to below pre-ACTH levels. Potassium loading (240 to 360 mEq. daily) produced two- to three-fold rises in aldosterone excretion and potassium restriction produced comparable falls. These changes could be prevented by inducing concomitant increases or decreases respectively in body fluid volume. Decreases of body fluid volume in normal subjects induced by dehydration, mercurial diuretics or sodium restriction consistently produced rises in aldosterone excretion; increases of body fluid volume in these subjects, induced by hydration (with pitressin to prevent diuresis) or by saline administration, lowered aldosterone excretion to or towards control levels.

Patients with cirrhosis and cardiac failure showed high initial aldosterone output despite pathologic expansion of body fluid volume. With the former group of patients, diuretics produced rises in aldosterone output, while in the latter group they sometimes produced falls as cardiac compensation was improved.

**Electric Activity of the Sinus Node, Atrial Myocardium and Atrioventricular Node**

*D. Durrer, Amsterdam, Holland*

The electric activity of the sinus node, atrial myocardium and atrioventricular node were studied with a cathode ray oscillograph and differential electrodes in 25 mongrel dogs. Temperature was carefully controlled.

Entirely negative complexes were seen in the unipolar leads of the pacemaker region of the sinus node. They did not have a smooth form; the descending limb of the P wave mainly showed many fine and coarse notches and they were constant from beat to beat. In the immediate region of this small area, the complexes were initially positive, but still predominantly negative, though less notched.

Differential complexes of the pacemaker region showed many very fast small-voltage deflections, coinciding with the notches in the descending limb. These were of approximately 15 msec. in duration. The remaining part of the sinus node region mainly showed the same differential complexes as the atrial myocardium.

In a few experiments 2 to 3 small low potential, low voltage fluctuations (0.05 mv., duration 3 msec.) were seen preceding the rapid spikes.

During atrial extrasystoles, evoked by electric stimulation of the atrium, the typical pattern in differential leads of the pacemaker region disappeared and a simply formed differential spike, of the same form as on the atrial surface, appeared. In the next beat originating in the pacemaker the multiple spiked complex appeared again. It is possible that the anatomic structure of the sinus node accounts for these findings.

The direction of propagation of the atrial activation was determined with differential electrodes. The differential spikes of the atriums showed a large fast complex, if the lead points were parallel with the direction of propagation of the activation wave and a small complex, if the lead points were placed perpendicular to this direction.

The findings thus obtained did not prove that the excitation wave spreads radially from the sinus node, but supported the hypothesis that the activation wave, originating from this node, spreads along the muscular ridges of the auricles so that the path of the activation wave is more or less curved.

The electric activity of the atrioventricular node was studied by means of differential needle electrodes introduced via the coronary sinus. In a small region differential complexes were seen of the same type as the sinus node and were constant from beat to beat. In the immediately surrounding atrial myocardium the normal differential spike of the atrial myocardium was seen. Pressure with the needle in this region resulted in complete or partial auriculoventricular block. Anatomic control, if possible, proved that the needle had been in the atrioventricular region. There was no essential difference in time relationships.

**Combination Therapy of Severe Hypertension with Ganglion Blockers and Reserpine**

*Harriet P. Dustan, A. C. Corcoran, R. Schneckloth and Irvine H. Page, Cleveland, O.*

We have proposed methods elsewhere for the evaluation of drugs used in the treatment of severe hypertensive disease. These involve accumulation of weekly averages of hospital or home-measured pressures, periodic clinical evaluation and establishment of overall therapeutic response in terms of a numerical severity index. Such longterm evaluations are complicated by spontaneous or induced changes in the course and rate of progress of the disease and by individual factors of situation, psychology, drug responsiveness and tolerance.

The precise evaluation of a single drug poses considerable difficulties which increase when drugs are used in combination, since each must also be studied singly. The study of these agents is basically empiric and their pharmacology is often obscure. These problems are exemplified by observations in 19 patients treated, usually in the first instance, with ganglion-blockers (hexamethonium, pentapyrrolidinium, Ecolid) and then with reserpine, alone and in combination. The effects of the combinations were determined in terms of supine and standing diastolic pressures, of daily requirements of the ganglion-blocker (a function of standing systolic pressure), of changes in the severity index and in terms of side-effects, notably, constipation. Constipation was symptomatically relieved in the majority of patients when using both drugs. Significant antihypertensive effects of the combination (decreases in supine or standing diastolic pressure and in daily blocker dose) were found in about one-third of the group; on further study, the majority of these responses were found to be sustained by and attributable to reserpine alone. The effects were not due to improved gastrointestinal absorption of the blocker during reserpine treatment, since they were also demonstrable in patients taking blockers parenterally. Rather, they seem attributable to the additive effects of the two drugs on neural functions which sustain blood pressure.

**Comparison of Gitalin with Digitoxin in Patients with Chronic Auricular Fibrillation**

*R. W. Dyke, C. Fisch and B. L. Martz, Indianapolis, Ind.*

This study was designed to compare the effects of recommended equivalent doses of gitalin and digitoxin on a group of patients with chronic atrial fibrillation, without regard to the etiology of the underlying heart disease.

Patients selected for this study had been on a maintenance dosage of digitoxin with satisfactory control of ventricular rate. Each patient was continued on his usual maintenance dose of digitoxin for the initial observation period of this study, which varied from 6 to 12 weeks. The patients were seen in the clinic at intervals, varying from twice a week to once every 2 weeks. Apical rate was determined after the patient rested in a chair for a minimum of 5 minutes and again immediately after 10 times stepping up on a 9-inch high-stool. These observa-

tions were recorded without reference to the patients' past performance. After the period of digitoxin control, the medication was changed to gitalin substituting 0.5 mg. of this preparation for each 0.1 mg. of digitoxin. Clinic observations for the subsequent 8 weeks were disregarded in tabulating the results, to assure adequate elimination of the digitoxin. The apical rates obtained during the next 6 to 12 weeks of observation were used in evaluating gitalin. In addition to observing the post-exercise rates, one-fiftieth grain of atropine was administered subcutaneously to 8 patients at the time the drug was either changed or the study discontinued. The effect of atropine on the apical rate was observed at 15-minute intervals for at least 1 hour. Seventeen patients were studied in the manner described above.

Analysis of the resting, post-exercise, and post-atropine average rates has indicated a statistically significant increase during the gitalin period.

The design of this experiment did not eliminate the possibility of progression of heart disease as a cause for higher apical rates during the gitalin period; however, clinically such progression was not evident. The many difficulties of assaying relative toxicity of the two preparations clinically are discussed.

**Hepatic Circulation and Function in Patients with Mitral Stenosis**

*John W. Eckstein, James W. Culbertson and George N. Bedell, Iowa City, Ia.*

In patients with congestive heart failure, a decrease in hepatic blood flow (EHBF) parallels the reduction in cardiac output and hepatic extraction ($E_{bsp}$) and plasma clearance ($C_{bsp}$) of bromsulfalein are diminished according to Myers. Patients, with mitral stenosis and not in heart failure, tend to have a low cardiac output. This study was undertaken to determine whether hepatic circulation and function are normal in such instances.

Twelve patients were studied, 6 had no systemic venous congestion (normal hepatic venous, right atrial and right ventricular end-diastolic pressure levels). Cardiac index (Fick) was low in 2 patients, low normal in 3 and normal in 1. Two patients had low normal hepatic blood flow, and 4 had normal values. Plasma clearance and hepatic extraction were low in 1 and normal in 5 subjects. Splanchnic oxygen consumption ($SpO_2$) was low in 1 patient, normal in 4 and was increased in one.

Two patients with mitral stenosis and not in heart failure (normal right ventricular end-diastolic pressure), but with tricuspid stenosis (elevated right atrial and hepatic venous pressure), had normal cardiac output and normal hepatic blood flow. Plasma clearance was subnormal in one and normal in one; hepatic extraction was normal in both patients. Splanchnic oxygen consumption was normal in one and was not determined in the other. Four patients with mitral stenosis and frank right ventricular failure had generally low values throughout.

These observations demonstrate normal hepatic circulation and function in patients with mitral stenosis and not in right ventricular failure. This shows that normal liver function may exist in the presence of mild central venous congestion. These findings confirm that there is a reduction of hepatic circulation and function in frank right ventricular failure.

**The Electrocardiogram and Right Ventricular Systolic Pressure in Patients with Valvular Pulmonic Stenosis and Intact Interventricular Septum**

*John W. Eckstein, L. E. January, James E. Odell and James W. Culbertson, Iowa City, Ia.*

The ECG and hemodynamic findings in each of 23 patients with proved valvular pulmonic stenosis and intact interventricular septum were reviewed critically for possible correlative diagnostic relationships.

ECG abnormalities were observed in 22 patients; right ventricular hypertrophy was diagnosed in 14 (time of onset of intrinsicoid deflection in right precordial leads = 0.03 second or more); 7 had incomplete right bundle branch block (QRS = rSR′ or rR′ in right precordial leads, septal activation assumed to be prolonged if the duration of r = 0.03 second or more); 1 had complete right bundle branch block. Of the 7 with incomplete right bundle branch block, 6 had evidence suggesting that this conduction defect was due to right ventricular hypertrophy (R′ > 10 mm., delay in activation of right ventricular free wall assumed if the duration of R′ = 0.03 second or more).

High R and deeply inverted T waves were observed in right precordial leads more frequently in patients with high right ventricular systolic pressure but occurred also in those with lower pressure levels. Delay in right ventricular free wall activation was found in 14 patients whose pressure ranged from 50 to 195 mm. Hg. In 8 patients with complete or incomplete right bundle branch block, the pressure ranged from 40 to 115. A normal ECG was obtained from one whose pressure was 110. Four different ECG diagnoses were represented among the 5 patients whose right ventricular systolic pressure was 110 or 115 mm. Hg. No consistent or reliable relationship was found to exist between the ECG and the right ventricular systolic pressure level.

Because a significant number of these patients had incomplete right bundle branch block (classified by the criteria of Myers), our data fail to support the concepts of systolic and diastolic overloading of the right ventricle as they relate to the ECG.

### Kinetocardiography and Ballistocardiography in Mitral Valve Disease

*E. E. Eddleman, Jr., Birmingham, Ala.*

Low frequency precordial movements and ballistocardiograms were studied in a group of patients with pure mitral stenosis and pure mitral insufficiency and correlated with clinical data.

Patients with mitral stenosis were found to have characteristic precordial movements. The most significant features of the records consisted of (1) an exaggerated early systolic outward movement of the precordium; (2) an exaggerated midsystolic outward movement of the precordium; (3) the anterior precordium is sustained out above the resting or diastolic level during the entire ejection phase in contrast to the marked retraction of the anterior precordium during ejection in normal subjects; (4) there is a marked inward movement of the precordium beginning in late systole and extending on through the early phases of diastole; (5) the apex thrust is markedly diminished or absent. A very consistent change in the ballistocardiogram (BCG) was the marked early systolic footward movement of the body (F-G downstroke), paralleling the initial outward movement of the precordium.

Kinetocardiographic tracings from patients with mitral insufficiency were characterized by (1) exaggerated early systolic retraction of the chest in the region of the apex; (2) prominent apex thrust; (3) a marked late systolic outward movement of the precordium. The BCG in patients with mitral insufficiency were not consistently altered. Thus precordial tracings in patients with mitral stenosis were consistently and markedly different from those noted in patients with mitral insufficiency. In addition, both tracings were consistently different from those noted in normal subjects. Postoperative tracings from patients with mitral stenosis often show a reversal of pattern back toward normal. Thus the kinetocardiogram appears to be an additional and valuable technic in the evaluation of the patient with mitral valvular disease before commissurotomy.

### Aneurysms of the Aortic Sinuses: Anatomic, Pathologic, Clinical and Physiologic Studies in Four Cases, in Three of Which Rupture Occurred

*Jesse E. Edwards, Luis M. Becu and Howard B. Burchell, Rochester, Minn.*

Four cases of aneurysm of the aortic sinuses have been studied from the anatomic, physiologic and clinical points of view. When the clinical picture has been characteristic, symptoms have appeared suddenly and a continuous murmur of the patent-ductus type has arisen. The anatomic aspects of the 3 aortic sinuses have been studied, so that the point of rupture of aneurysms of the various sinuses is clearly demonstrated. As to pathogenesis, studies of longitudinal sections of the aortic sinuses indicate that the main feature is a separation of the aortic wall from the *annulus fibrosa* of the aortic valve. The frequent association of a ventricular septal defect is of importance, both from the clinical and the pathologic viewpoint. The small apertures in the aneurysm of the aortic sinus, which are responsible for the heart failure, may be emphasized. Details of the clinical histories, roentgenograms, electrocardiograms, and cardiac-catheterization data concerning the 3 patients in whom rupture of the aneurysm occurred is presented. In 2 cases the posterior aortic sinus was involved and in 1 case the right aortic sinus was involved. The importance of these basic studies to potential surgical therapy for this condition is believed evident.

### Chlorpromazine in Combination with Rauwolfia in the Treatent of Essential Hypertension

*Harold B. Eiber, New York, N. Y.*

The use of various combinations of hypertensive agents in the treatment of essential hypertension is commonly accepted therapeutically. An attempt at attenuation of undesirable side effects and toxicities of the more potent hypotensive agents is made by combining smaller dosages of the latter with milder agents; e.g. *Rauwolfia serpentina* and hydralazine. In spite of this theoretic solution, side effects are present and unpredictable while dosage schedules are cumbersome. Effective therapy is frequently limited to hospitalized patients. Smaller dosage schedules, not productive of side-effects, are generally ineffectual in the control of hypertension.

In a 2-year study of essential hypertension, 250, mostly ambulatory, patients aged 19 to 93 years were treated for a period of 3 to 18 months with an oral combination of chlorpromazine (Thorazine) and the crude root of *Rauwolfia serpentina*. The combination of these two agents appears to exert an interrupting effect on the corticothalamic tracts, producing gradual, but effectively sustained control of hypertension without significant side effects.

Results with the combination of Thorazine and *Rauwolfia serpentina*: In grade 1, normotension was achieved in 95 per cent of cases; in grade 2, normotension, in 51 per cent of cases; and in grade 3, mean blood pressure of less than 130 mm. Hg, was attained in 35 per cent of cases. All of the patients had marked symptomatic relief within 10 to 14 days. There were no significant side effects and no signs of toxicity. Cardiac enlargement, renal function and retinal pathology were significantly reduced.

It appears that the combination of the crude root of *Rauwolfia serpentina*, which is only a mild hypotensive agent, with chlorpromazine, hitherto never employed as a hypotensive agent, is superior to other drug combinations for the safe effective con-

rol of essential hypertension. Similarly, the same ombination of agents has proven more beneficial han the use of either agent, given singly, in various ormotensive neuropsychiatric patients.

**Cerebral Vascular Thrombosis as the Presenting Manifestation of Acute Myocardial Infarction**

*Maurice Eliaser, Jr. and Henry A. Avon, San Francisco, Calif.*

A group of 65 patients hospitalized with the admitting diagnosis of cerebrovascular disease was reviewed. An analysis was made of the relationship between cerebral vascular thrombosis and presumably otherwise silent myocardial infarction.

Cases were selected to exclude nonthrombotic cerebral vascular disease and those with histories that indicated manifestations of coronary artery disease within a period of several days prior to or in association with the cerebral episode. If ECG data necessary for proper evaluation was lacking, the cases were omitted. The remaining 24 cases, otherwise unselected, were additionally studied and revealed the following data: 19 patients had been unable to give adequate history of the events immediately preceding hospitalization because of coma, motor aphasia or other depression of cerebration and 11 had documented evidence of arterial hypertension, antedating the cerebral vascular attack. ECG study revealed that 10 patients (41.7 per cent) had incurred an acute myocardial infarction either prior to or in association with hospitalization for the cerebral thrombosis; the records of 12 patients (50 per cent) showed uncomplicated left ventricular enlargement. One record (4.1 per cent) was classified as revealing subendocardial ischemia without definite evidence of acute infarction and one (4.1 per cent) showed borderline changes suggesting myocardial damage of indeterminate duration. Of 7 patients who died, 2 were examined post mortem and each revealed an acute cerebral thrombosis and acute coronary thrombosis associated with myocardial infarction. The remaining five had ECG changes indicative of recent myocardial infarction.

The frequent coexistence of cerebral thrombosis with myocardial infarction or left ventricular enlargement indicates the importance of ECG investigation of all cases with cerebral vascular attacks, especially those whose lesion of the central nervous system preclude an adequate history. Acute hemiplegias may be considered an additional but not uncommon manifestation of socalled silent myocardial infarction. The management of the patient with an acute cerebral thrombosis is significantly altered by the knowledge of the presence of a recent myocardial infarction or left ventricular strain, especially if physical therapy is contemplated.

**The Use of Intravenous Ganglionic Blocking Agents for Acute Pulmonary Edema**

*Myrvin H. Ellestad and William H. Olson, Long Beach, Calif.*

For many years efforts to decrease venous return to the heart have been effectively used in acute congestive failure or pulmonary edema. These include use of phlebotomy, Fowler's position, tourniquets, digitalis and many others. In basic research programs, Sarnoff, Helden, Freis and others have used ganglion blocking agents with success in the treatment of pulmonary edema. These, however, were not recommended for clinical use; in fact, Helden claimed it was not safe after trying it in 7 cases. It is our purpose to discuss the place of this method in clinical medicine and to establish it as a safe and useful therapeutic concept.

When acute congestive failure develops, certain physiologic conditions usually occur. They are (1) reflex increase in peripheral resistance with resultant increase in systemic blood pressure; (2) increased venous pressure, right heart filling pressure, pulmonary artery pressure and transudation of fluid into the alveolar spaces; (3) hyperpnea with decreased ventilatory efficiency; (4) probably decreased left ventricular output (with reference to the right ventricle); (5) marked anxiety and (6) arterial anoxia. Ganglion blocking agents tend to return (1) to (4) towards normal, especially, if the systemic arterial pressure is markedly elevated.

Over 20 cases of acute pulmonary edema have been studied at this time. In most of these cases all of the conventional methods of therapy were withheld for at least a half-hour. If after this time no improvement occurred, the conventional therapeutic measures were used. In all but 2 cases, however, response to the intravenous ganglionic blocking agent, usually hexamethonium 2.5 mg., was excellent. The patient had a rapid decrease in venous pressure as well as peripheral arterial pressure. The hyperpnea decreased markedly and the anxiety and degree of pulmonary congestion resolved very rapidly. Many of the cases were completely free of symptoms and relaxed and ready to lie down and go to sleep within 15 or 20 minutes. It seems from this preliminary study that this will be a dramatic adjunct to treatment of this very serious condition.

**A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis**

*H. Engelberg, R. Kuhn and M. Steinman, Los Angeles, Calif.*

The injection of adequate amounts of heparin results in a marked reduction of the low density serum lipoproteins and has been reported to retard the development of atherosclerosis in cholesterol-fat fed animals. Evaluation of the results of heparin

therapy on the course of human atherosclerosis is therefore important. Studies of its effect upon angina (a subjective manifestation of pre-existing disease which is hard to evaluate) have been contradictory and highly controversial. We felt it was desirable to observe the objective manifestations of progress of the disease in a group of patients with advanced coronary atherosclerosis.

Accordingly, over 200 patients who had each sustained a myocardial infarction in the past were alternately placed into 2 groups. All patients had a preliminary ECG, ballistocardiogram, serum cholesterol and ultracentrifugal lipoprotein determinations. One group received 200 mg. of concentrated aqueous heparin, subcutaneously twice weekly, the minimum believed necessary to produce a substantially decreased average concentration of the low density serum lipoproteins. The other group received 1 cc. of isotonic saline, subcutaneously twice weekly. In all other respects therapy was identical. Fat restriction was not prescribed.

Within the past 2 years the placebo group of 81 men and 37 women (average age 61.6 years) received 2191 months of therapy (average 18.6 months per patient). There were 21 deaths due to cardiovascular disease in this control group. The heparin group of 73 men and 32 women (average age 62.6 years) received 2067 months of therapy (average 19.7 months per patient). In this group there were 4 deaths due to cardiovascular disease. The observed difference in deaths is statistically significant ($p = .01$). These results indicate that heparin, in the dosage and manner administered, markedly retards the progress of cardiovascular disease in patients with coronary atherosclerosis.

**Results of Medical Management of Coarctation of the Aorta Diagnosed in Infancy**

*Mary Allen Engle and Henry P. Goldberg, New York, N. Y.*

Coarctation of the aorta was diagnosed in 23 infants between 2 weeks and 5 months old. They were followed up for the past 7 years. Heart failure was present in 18, when first examined. Common to all but one were feeding difficulty and failure to gain weight. Respiratory distress, episodes of cyanosis and attacks of pallor and perspiration were frequently noted.

The diagnosis was based on the presence of a strong pulse and an elevated blood pressure in an upper extremity which contrasted with a feeble or impalpable pulse and a low or unobtainable blood pressure in the legs. Blood pressures in the arms ranged from 170/110 to 120/70 mm. Hg on admission. A systolic murmur was present in all and a gallop rhythm was detected in all but 3 of the babies. Roentgenograms revealed enlargement of the left and often of the right side of the heart, and ECGs indicated enlargement of one or both ventricles.

Management was directed toward the correction of cardiac failure, toward the regulation of feedings and prevention of infection. Surgery was planned immediately if medical management failed. Of the 23 patients, 13 had uncomplicated coarctation and 10 had coarctation, complicated by intracardiac lesions.

In the group uncomplicated by lesions other than temporary patency of the ductus arteriosus, heart failure responded promptly and did not recur. By the age of 1 year, specific therapy has been discontinued in all but 1 patient and symptoms have disappeared. Growth and development have become normal. Blood pressure levels have fallen, in some instances to normal, and femoral pulses have become faintly palpable in some. The cardiothoracic ratios have diminished and in none is there persistence of left atrial enlargement. Abnormalities of the T waves have disappeared from the ECG and evidence of ventricular hypertrophy has lessened. In several, the ECG has become normal. Surgery has not yet been performed and is considered to be no more urgently indicated in this group than in asymptomatic children, first seen beyond the age of infancy. In the group with complicating lesions, there were 7 deaths. Ventricular septal defects and endocardial fibroelastosis were frequent findings at postmortem examinations. The three survivors responded less promptly and required digitalis for longer periods than did the clinically uncomplicated group.

Our experience with the beneficial effects of nonsurgical management of the difficulties encountered during early infancy by some patients with coarctation of the aorta leads us to believe that medical therapy should be the first choice for such infants and that it is usually effective. Surgery can then be safely postponed until an age when the aorta has more nearly reached adult proportions, but has not yet developed degenerative changes.

**The Clinical Picture of Aneurysm of the Abdominal Aorta**

*Charles D. Enselberg, New York, N. Y.*

This report is an attempt to clarify the diagnostic picture of abdominal aortic aneurysm, based on an experience with 34 proven cases. In this group, correct clinical diagnosis (including x-ray diagnosis) was made in only 16. There were 29 males and 5 females; 1 patient was 22 years old, 9 were between 52 and 57, 14 between 60 and 69, 9 between 70 and 79, 1 patient was 86 years old. The diagnosis in 32 patients was arteriosclerosis, in 1 case, syphilis and in 1, the etiology was considered congenital. Of these 34 patients, 26 died and 19 were autopsies. Follow-up studies are in progress on the 8 survivors. Rupture of the aorta occurred in 14 cases, in 6 of which this diagnosis was missed. No patient survived rupture and only 3 could be subjected to reparative surgery.

The most common symptoms associated with ab-

ominal aortic aneurysm were lower backache usually on the left side), low abdominal pain and ain simulating renal colic. Referral along the posterior thigh occurred in a few. Only 5 patients had no symptoms explainable on the basis of aneurysm.

A palpable abdominal mass was found in 21 cases. In 16, the mass exhibited expansile pulsations, and in 15 it was tender. Murmurs and thrills were noted in 5 and 4 cases, respectively. In only one instance was it specifically noted that the mass was not tender. In the author's experience with another group of cases where the pulsating mass proved to be a buckled but not aneurysmal aorta, tenderness was not elicited. X-ray examination revealed calcified outlines of the aneurysmal wall in 12 cases. In 7 instances aortography was diagnostic. In 4 cases indirect signs were found, such as a soft tissue mass or displacement of the kidney and ureter were noted on pyelography. The 14 patients with rupture all presented the classic picture of hemorrhagic shock. In almost every case a history was obtained which pointed to retroperitoneal involvement (severe backache, "renal colic"). Reflex ileus was common in patients surviving 2 days. However, 9 of the 14 died within 48 hours. In 4 cases it seemed probable that small extravasations had occurred weeks or possibly months before the major catastrophe. Rupture was usually through the posterolateral aspect of the aorta into the retroperitoneal space. Intraperitoneal hemorrhage was found only twice. In 2 cases, rupture occurred in associated thoracic aneurysm whose presence was unsuspected.

From this experience it seems justified to stress (1) tenderness of a pulsating abdominal mass, (2) x-ray disclosure of calcified outlines of the aneurysmal wall and (3) hemorrhagic shock preceded by "renal colic" or unusually severe low back pain as valuable aids in establishing the clinical diagnosis.

### Body Sodium and Water in Patients with Heart Disease

*Saul J. Farber and Robert J. Soberman, New York, N. Y.*

A prominent disorder in the syndrome of congestive heart failure is salt and water retention. This abnormality may be associated with other metabolic defects occurring in heart disease. In an attempt to find a relationship between salt and water retention and other metabolic defects in congestive heart failure, it was felt that at first, the relative amounts of salt and water in patients with this disorder should be determined. The data indicate that patients in the edematous phase of heart disease have relatively more exchangeable Na than water in their bodies. This is not the situation in patients with edema due to liver or renal disease. Moreover, after patients with edema due to heart disease are rendered edema free, they still have an abundance of Na over water in their bodies.

Exchangeable Na was determined by isotope and body water by antipyrine dilution. In 9 patients with edema due to heart disease, body water as determined by antipyrine and by deuterium were in close agreement. The following results expressed as sodium milliequivalents (Na mEq.) per liter of body water were obtained: 27 normals, 81 mEq.; 50 edematous patients with heart disease, 108 mEq.; 16 with liver disease, 90 mEq.; 10 with renal disease, 89 mEq.; 33 patients with heart disease who were previously edematous, 100 mEq.

These results show that in heart disease there apparently is a metabolic defect that leads to the accumulation of an abundance of Na in relation to water. This could be due to one or several of the following defects, (1) an excess of intracellular sodium; (2) storage of sodium in a solid depot, such as bone and/or cartilage or (3) sodium binding to some polyelectrolyte constituent of the body, an example of which would be mucoproteins.

### Hemodynamic Patterns in Congestive Heart Failure

*M. Irené Ferrer, Réjane M. Harvey, André Cournand and Dickinson W. Richards, New York, N. Y.*

Although there are many ways of discussing and describing congestive heart failure, the authors have chosen to present several different hemodynamic patterns encountered in patients with clinical congestive heart failure, in order to illustrate its complexity as well as to provide certain concepts about this condition.

The hemodynamic picture of left ventricular failure can be distinguished from that of right ventricular failure and this distinction is further emphasized by the response to digitalization. Although the hemodynamic pattern, encountered in combined right and left ventricular failure of recent origin with normal sinus rhythm, resembles that of combined failure of long standing, the degree of hypervolemia and acute digitalization studies may differentiate them. Patients with atrial arrhythmias and combined ventricular failure offer some interesting contrasts to those in failure with sinus rhythm. Despite clinically comparable degrees of heart failure, pulmonary hypertension and pulmonary pulse pressure are considerably less in patients with arrythmias than in patients with sinus rhythm.

From the data presented, it appears that the heart in congestive failure is characterized by a cardiac output which is lower than it was prior to the onset of failure, although the actual level may still be in the normal range. It is further characterized by an increase in diastolic pressure in the failing ventricular chamber. Furthermore, in the forms so far studied, the failing heart responds to digitalis bodies by an increase in cardiac output and a fall in diastolic pressure. The pressure changes in the pulmonary bed are dependent in some measure upon the total pulmonary blood volume, the size of the stroke volume, pulmonary vascular changes and other

causes of pulmonary hypertension. Finally, a preclinical stage of heart failure has been identified and is seen in the asymptomatic patient who nevertheless gives physiologic evidence of congestive phenomena at rest or during exercise.

**Hypertension and Pyelonephritis Masquerading as Toxemia of Pregnancy: An Analysis of 1051 Cases**

*Frank A. Finnerty, Jr., Washington, D. C.*

Serial studies on 1051 "toxemia suspect" patients have revealed that hypertensive vascular disease and pyelonephritis frequently masquerade as toxemia of pregnancy. The triad of (or any part of) an elevated blood pressure, edema and albuminuria have been seen in each of these diseases. Experience has suggested that ophthalmoscopic examination and a complete urinalysis permit prompt differentiation of these diseases.

Toxemia is said to exist when the ophthalmoscopic examination reveals a retinal sheen and normal arteries and urinalysis reveals only albuminuria. Hypertensive vascular disease exists when the retinal arteries show hypertensive changes and no retinal sheen is present. When both hypertensive changes and a retinal sheen are seen on ophthalmoscopic examination with or without albuminuria, toxemia is then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggests pyelonephritis; clumps of white cells and glitter cells document the diagnosis. Though a retinal sheen and albuminuria are seen both in toxemia and acute glomerulonephritis, microscopic hematuria (occasionally gross hematuria) is seen more commonly in glomerulonephritis.

Though 95 per cent of the patients, referred to the clinic, were originally diagnosed as toxemic, only 13 per cent had toxemia by our criteria. Our diagnoses included hypertensive vascular disease (666), hypertensive vascular disease plus superimposed toxemia (90), post partum hypertension (72), pure toxemia (154), pyelonephritis (56), edema without disease (8) and unrelated cardiac or renal disease (5).

The ability to differentiate these disease states provided the opportunity to study whether or not toxemia caused vascular damage. Of the pure toxemia group, 125 patients revealed no abnormality 6 weeks post partum. In 29, however, despite return of the blood pressure to normal and disappearance of edema and albuminuria, examination of the retina revealed definite retinopathy. These retinal changes are attributed to the duration of the toxemia rather than to its severity.

**Heart in Dystrophia Myotonica**

*Charles Fisch, Indianapolis, Ind.*

Accumulated evidence suggests that a definite but poorly understood relationship exists between the basic pathology of the various myopathies and the high incidence of heart disease in these disorders.

This presentation deals with the heart in *dystrophia myotonica*. In a series of 85 cases collected by the author the ECG was abnormal in 70 per cent, other abnormalities consisted primarily of cardiac enlargement and evidence of failure. Anatomic studies of the heart were very meager. Of the 9 cases studies personally, 6 showed definite cardiac abnormality, consisting of atrial flutter in 2, prolonged P-R interval in 2, nonspecific T wave changes in 1 and left bundle branch block with marked cardiac enlargement in 1.

One of the patients died of acute heart failure, and we were afforded the unusual opportunity to study the heart anatomically. The coronary vessels were patent and free of any atheromatous plaques. The myocardium showed extensive fibrosis with disintegration of some and hypertrophy of other muscle fibers. Unusual large rectangular muscles were present in some of the muscle fibers.

**The Electrocardiogram in Persons Over Seventy Years of Age**

*Charles Fisch, P. D. Genovese, R. W. Dyke, W. Laramore and R. J. Marvel, Indianapolis, Ind.*

The ECG in the aged has been described a number of times. Most of the studies were confined to the three limb leads and in some series one chest lead was included. A review of the data disclosed a failure to apply uniform criteria of normalcy when interpreting the tracings and lack of agreement as to the frequency of various abnormalities.

Five-hundred ambulatory individuals in nursing homes and a State mental institution were examined by 5 internists; 250 also had a chest roentgenogram. A 12-lead ECG was obtained, using a direct writer. The ECG was considered normal when it satisfied the criteria set by the New York Heart Association. Hypertension was defined as any reading above 140 mm. Hg systolic and 90 mm. Hg diastolic.

Of the 500 ECGs, 216 (43.2 per cent) were normal, 80 (16.0 per cent) exhibited an occasional premature systole and 204 (40.8 per cent) were abnormal. The major abnormalities were nonspecific ST-T changes in 87 (42.6 per cent), right bundle branch block in 31 (15.2 per cent); prolonged P-R interval in 21 (10.3 per cent); atrial fibrillation 19 (9.3 per cent); left bundle branch block 15 (7.4 per cent), I-V conduction defect in 12 (5.8 per cent); myocardial infarction in 12 (5.8 per cent); atrial tachycardia in 3 (1.4 per cent); nodal rhythm in 2 (.9 per cent); A-V dissociation in 1 (.4 per cent) and wandering pacemaker in 1 (.4 per cent).

The incidence of cardiac disease, exclusive of hypertension, accompanying the various ECG disturbances, was left bundle branch block in 46.6 per cent; non-specific ST-T changes in 40.2 per cent; atrial fibrillation in 40.0 per cent; I-V conduction

defect in 25 per cent; premature beats in 20 per cent; RBBB in 15.1 per cent and prolonged P-R interval in none. There was no difference in the incidence of the abnormal ECG in the hypertensive and the normotensive group.

The incidence of the abnormal ECG was twice as high in the group with detectable heart disease as in the group without detectable heart disease. However, the abnormal ECG was accompanied by clinically detectable heart disease in only 38.7 per cent of the cases. There is a marked discrepancy between the number of abnormal ECGs with clinically detectable heart disease and the "normal" ECG in the aged, compared to the ECG in younger individuals.

**Left Heart Catheterization by Means of Transthoracic Left Atrial Puncture**

*Don L. Fisher and Maurice H. McCaffrey, Pittsburgh, Pa.*

Left heart catheterization has been used in the diagnostic study of over 80 patients. Nearly all had serious rheumatic valve disease with atypical findings and were being considered for surgery.

A transthoracic left atrial puncture was performed by the right paravertebral approach, after mild sedation and procaine infiltration of skin and subcutaneous tissues. The prone position was used, with intermittent fluoroscopy for guidance in inserting the 6 inch #18T needle. After atrial puncture, a plastic catheter was inserted through the needle, for access to the left ventricle and aorta, where additional pressure recordings were made. The needle was then removed, leaving the flexible catheter in place in the left atrium. Then the patient turned to the supine position for cycling exercise.

Diagnostic standards for interpretation of pressure recordings were derived from previous studies of pressures during valve surgery. The severity of mitral stenotic obstruction was indicated by the amount of pressure drop across the valve, during ventricular diastole. Mitral insufficiency was measured by the amplitude of the regurgitant pulse into the left atrium during ventricular systole. This pulse was not always evident when the mean atrial pressure was under 20 mm. Hg. The severity of obstruction in aortic stenosis was indicated by the amount of the pressure drop across the aortic valve during the ventricular systolic pulse. Aortic insufficiency was not studied. Ventricular failure from any cause resulted in increased diastolic pressure.

These diagnostic standards were applied to the series of tests, with grading of severity of the valve lesions. The results showed no major disagreements with later findings at 26 operations and 8 autopsies. Complications of the test included 1 pneumothorax, 2 hemothorax, and 1 hemopericardium with tamponade effects. No fatalities nor lasting sequelas resulted. This test gives reliable diagnostic information and its use should be continued.

**Physiologic Response to the Master Two Step Test in Normal Males**

*Amasa B. Ford, Herman K. Hellerstein, William K. Littman, James L. Phillips and Aristides Gousios, Cleveland, O.*

The physiologic response to the Master two-step test, of 116 males, without known cardiovascular disease, has been measured. The energy cost, oxygen consumption, ventilation and "oxygen utilization" were determined, in addition to ballistocardiograms at rest, blood pressure, pulse rate and ECGs before and after exercise.

Thirty-five subjects (30.2 per cent) were eliminated from the control group because (1) hypertension or an abnormal ECG at rest in 14 subjects; (2) abnormal ECG response to exercise in 4; (3) delayed recovery of blood pressure after exercise in 14 and (4), both abnormal responses in 3 subjects. The final, strictly normal control group consisted of 82 subjects, 20 in each decade from 20 to 50 years, 18 from 50 to 59 years, and 4 subjects from 60 to 69 years.

The amount of step-climbing prescribed by the Master two-step test depends upon weight and age. Work performed in raising the body decreased significantly ($p = <0.01$) with age from an average of $510 \pm 55$ Kg. per M. per minute in the third decade to $346 \pm 60$ Kg. per M. per minute in the seventh. Oxygen consumption above resting, however, did not change significantly with age, averaging $1.48 \pm 0.19$ L. per minute of exercise (5.8 times resting). The oxygen cost of exercise was about equally divided between the exercise and recovery periods, with a ratio of 1.17 to 1, and did not vary significantly with age. Seventy-one per cent of the oxygen debt was repaid by 1.5 minutes after exercise and 88 per cent by 3.5 minutes. "Oxygen utilization" at rest (milliliters of oxygen extracted per 100 ml. of air breathed) was greater in subjects below the age of 40 ($p = <0.001$) and showed a greater increase during exercise ($p = <0.01$).

A significant proportion of a presumably normal male population shows evidence of cardiovascular dysfunction at rest or during brief, moderately severe exercise such as the Master two-step test. The amount of external work performed at a given oxygen consumption decreases with aging. "Oxygen utilization" decreases above the age of 40, while other physiologic functions do not change significantly.

**Influence of an Oscillating Bed on Blood Flow and Oxygen Tension of Ischemic Toes**

*Carlos Forno, Philadelphia, Pa.*

The following studies were made to learn the optimal mechanical adjustment and timing of an oscillating bed needed to produce an increase in digital blood flow, as measured by rise in skin temperature,

and also an increase in digital oxygen tension, as measured polarographically.

Sixty-four experiments were performed; 16 different experiments were conducted upon each of 4 patients having severe arteriosclerosis obliterans. Eight skin temperature studies were made in a thermoregulated room on 4 toes of one leg, readings being recorded at 2-minute intervals; 4 of these studies had the extreme foot-down adjustment of the bed at a 12 degree angle and 4 at a 20 degree angle. These angles were held stationary for 12 seconds, 1, 2 and 5 minutes respectively. Eight oxygen tension studies were made by means of the open-type platinum electrode, an electrode being inserted at the base of the same 4 toes, and galvanometric determinations taken at 5-minute intervals. The same angles and timing cycles were used as in the first series. A 5-degree, extreme foot-up position, stationary for 12 seconds, was maintained throughout all 64 experiments. The oscillation period averaged 44 minutes for each experiment. There were 2 control periods of approximately 20-minutes each with the bed horizontal, 1 preceded and 1 followed the oscillation period.

There was an appreciable increase in both skin temperature and oxygen tension when the bed was adjusted at a 20-degree, extreme foot-down position for 5 minutes. This was the only combination in which there was a significant increase in either skin temperature or oxygen tension. The therapeutic implication is apparent.

### Simple Formulas for Study of Circulatory Dynamics

*John H. Foulger, Wilmington, Del.*

Diameters ($d_b$) of the ascending aorta tabulated by Bazett from Suter's autopsy data are fitted by a formula based on age ($A$), body surface area ($S.A.$), pulse rate ($R$) and median arterial blood pressure ($M.B.P.$). The ratio of calculated diameters ($d_c$) to Bazett diameters ($d_b$) falls with rising diastolic pressure ($D$). This accords with Wiggers' observation that the distensibility of the dog's aorta decreases during acute hypertension induced by drugs.

$$d_c = \sqrt{A(S.A.) \cdot \frac{\sqrt{R}}{M.B.P.}}$$

$$\text{and} \quad \frac{d_c}{d_b} = (1.3419 - 0.0041D)$$

These 2 formulas can be combined. Since $A$, $S.A.$, and $d_b$ are constant for a given subject at a given time, relationships between $R$, $D$ and $M.B.P.$ can be deduced and used to analyze trends in circulatory dynamics caused by physical exercise, drugs, the Flack test, occlusion of A-V fistulas and related processes.

Physical exercise (bicycle ergometer 540 Kg. per minute for 35 minutes, plus 900 Kg. per minute for 2 minutes) did not disturb the expected trend in $R$, $D$ and $M.B.P.$ But during rest, 18 minutes later, $R$ remained unexpectedly high and $M.B.P.$ fell.

Intravenous *l*-epinephrine (1732 mg. in 7.3 minutes) does not disturb the expected pattern. But intravenous *l*-norepinephrine (770 mg. in 2 minutes) depresses $R$ and increases $M.B.P.$, reversing the pattern. Roxinil, in therapy for hypertension, depresses $R$, whereas a rise in $R$ is predicted from the change in $M.B.P.$ and $D$. Compression of A-V fistulas (femoral, subclavian or carotid) caused the expected increase in $D$ and $M.B.P.$ but unexpectedly depresses $R$. The Flack test increases $R$ and $D$. Our formulas would predict a fall in both. These examples illustrate a new type of analysis of data collected by simple procedures.

### Use of Methylene Blue as an Indicator for Arterial Dilution Curves in the Study of Heart Disease

*Irwin J. Fox, William P. Crowley, Jr., Joseph B. Grace and Earl H. Wood, Rochester, Minn.*

Methylene blue has been tried as a substitute for T-1824 to avoid bluish discoloration of the skin resulting from the multiple doses of Evans blue required for localization and quantitation of intracardiac shunts during cardiac catheterization. Dilution patterns were recorded by earpiece and cuvette oximeters after successive injection (on the average, 6 minutes apart) of similar doses of both dyes in 16 patients with heart disease and in 6 normal persons.

The time components of methylene-blue curves in normal persons were similar to those for T-1824; however, in equal doses, methylene blue produced a peak deflection 1.8 (1.7 to 2.0) times greater than Evans blue. Thirty seconds after the peak deflection the concentration of methylene blue in arterial blood decreased to 2.8 (1 to 4) per cent of the peak as compared to 16.0 (12 to 20) per cent for T-1824, while simultaneously these concentrations at the ears averaged 15 and 18 per cent for methylene and Evans blue, respectively. These findings, along with the reduction or absence of a systemic recirculation peak in methylene-blue curves, demonstrated its rapid loss from the blood stream to the tissue.

By means of the ear oximeter, methylene blue was uniformly demonstrated in "bloodless tissue" (pressurized ear) 2.4 (1 to 4) minutes after the intravenous injection (0.1 to 0.3 mg. per Kg. of body weight), while T-1824 could not be detected in bloodless tissue after similar periods.

Comparison of the contours of arterial curves from 9 patients with left-to-right shunts reveals the degree of prolongation of the disappearance slope, typically seen with T-1824 to be diminished in methylene-blue curves. Dye concentrations in arterial blood at 20 and 30 seconds, respectively, averaged 14 and 9 per cent of peak concentration,

compared to 42 and 34 per cent for T-1824. In this study, methylene blue has proven to be a suitable indicator for the detection and localization of right-to-left shunts.

**Malformations of the Heart and Great Vessels of Rats with Experimentally Induced Congenital Transposition Complexes**

*Marjorie H. Fox and Charles M. Goss, New Orleans, La.*

Fourteen pregnant rats of a Long-Evans substrain were injected subcutaneously with 1 ml. of a 1 per cent aqueous solution of trypan blue eight and a half days after insemination and sacrificed 10 or 11 days later. Dissection of the 89 fetuses recovered from these females revealed that 31 (35 per cent) had some degree of transposition of the major arterial trunks, from 10 to 66 per cent of each litter being affected. None of 164 fetuses, recovered from uninjected control dams, had this type of cardiovascular abnormality.

The 4 major types of transposition complexes in the fetuses occurred as follows: Overriding aorta in 13; partial transposition in 5; overriding pulmonary trunk in 6; complete transposition in 7.

All but 2 of these abnormal fetuses had a high interventricular septal defect, 25 had both atrial appendages and, to a lesser degree, the atria shifted to the right or left of the great vessels and 17 had additional aortic arch abnormalities. Of the 18 specimens with aortic override or partial transposition, 13 had a subpulmonary stenosis which was frequently accompanied by hypoplasia of the pulmonary trunk. Complete aortic transposition invariably resulted in a counterclockwise rotation of the aortic valve and alterations in coronary artery distribution.

The resemblance of many components of these experimentally produced complexes to those of clinically important human congenital syndromes, as the tetralogy of Fallot and the Eisenmenger and Taussig-Bing complexes, is striking. Consequently, not only does the trypan blue technic afford a method of experimental attack on the problems of mammalian cardiovascular development, but conceivably projected studies on the pre- and postnatal development of trypan blue exposed fetuses will also prove to be of value to the clinician and cardiac surgeon.

**Precordial Vectorcardiography**

*Ernest Frank, Philadelphia, Pa.*

Lead vectors of currently used systems of spatial vectorcardiography suffer from various quantitative defects, as demonstrated by experiments with accurate three-dimensional torso models. It is found that these lead vectors are not parallel to anatomic body axes, are not orthogonal, are unequal in length and improperly corrected and, most serious, are susceptible to equivalent heart dipole location errors which are different for each individual. A new improved system of vectorcardiography utilizing 7 electrodes, several of which are placed on the precordium, is practical for clinical use. This system is proposed as an optimum compromise among many conflicting factors including soundness of theoretic basis, accuracy, reproducibility and speed of application. For dipole locations within a 25 square centimeter area in the transverse plane (estimated to encompass 90 per cent of subjects), lead vectors of this system are accurate to $\pm 4$ degrees in angle and $\pm 20$ per cent in length in torso models. This represents a substantial improvement over present systems, especially regarding invulnerability to dipole location errors. Experiments indicate that comparable accuracy is obtainable in most humans for the QRS complex.

In applying this system, the transverse level of the heart is first determined by a novel triple-electrode precision technic. Five electrodes are then placed around the chest in accurately designated anatomic locations from which data are derived for determination of transverse dipole components. Data for the head to foot dipole component are determined from electrodes on the neck and left leg. Potential differences from all electrodes are automatically processed by simple resistive adding networks in the vectorcardiograph, yielding 3 orthogonal components of equal normalization for convenience in amplification. The entire procedure may be routinized, requiring approximately 15 minutes per subject. Resultant components average twice the size of those in current systems and give improved performance concerning muscle tremor and 60 c.p.s. interference.

**Effects of Mecamylamine in Hypertensive Patients**

*Edward D. Freis and Ilse M. Wilson, Washington, D. C.*

Mecamylamine hydrochloride, according to Beyer, is a ganglionic blocking agent, completely absorbed from the gastrointestinal tract of animals. In 14 hypertensive patients given dosages of 10 to 30 mg. either intravenously or orally on subsequent days, we have found almost identical hypotensive effects.

After hypotensive doses of mecamylamine intravenously, digital plethysmography failed to reveal significant inhibition of vasoconstrictor reflexes. Abolition of the skin temperature gradient from toe to umbilicus in a cold room usually was incomplete. Thus, inhibition of vasoconstrictor reflexes was less marked in comparable hypotensive doses than with hexamethonium.

Thirty-five hypertensive patients (2 with grade I; 17, grade II; 12, grade III; and 4 with grade IV fundi) have been treated with oral mecamylamine for periods up to six weeks. Mean reduction of basal

blood pressure in the supine position was 23 per cent systolic, 19 per cent diastolic, and in the erect position 30 per cent systolic and 23 per cent diastolic. The mean total daily dose was 30 mg. (range 8 to 80). No evidence of tolerance was seen.

Side effects, observed primarily during early dosage adjustment, were as follows: mild ileus in 3; controllable constipation in 31; dryness of the mouth, severe in 1 and mild in 7; paresis of visual accommodation, moderate in 4 and mild in 4; postural faintness, severe in 5 and mild in 3; mild paresis of the urinary bladder in 6 and impotence complained of in 2.

Mecamylamine is the first potent ganglionic blocking agent which is completely absorbed from the gastrointestinal tract of man. With careful dosage adjustment, 24 hour control of blood pressure has been possible on 3 to 4 small doses per day. Tolerance has not yet appeared and side effects are no more prominent than with other ganglion blockers.

**The Multiphasic Nature of Blood Flow, Velocity and Vascular Volume in the Upper Extremity of Man**

*Edward D. Freis, Harold W. Schnaper, Lawrence S. Lilienfield, Ilse M. Wilson and Renato Kovach, Washington, D. C.*

Instantaneous injection of 1.5 mg. of the dye T-1824 into the brachial artery resulted in significant concentrations in the effluent veins, while dilution made the total body concentrations negligible. Thus, dye washout in the injected extremity was determined without significant contamination from recirculation. Washout patterns were determined in 24 normal subjects and 3 patients with congestive heart failure.

The washout of the dye concentration curve usually was biphasic with an early steep downslope representing high velocity components and a later shallow downslope of the low velocity portions. $Cr^{51}$ tagged red blood cells gave similar results in 6 additional cases. Local hyperemia produced a single steep downslope. In venous congestion the slow component predominated.

The flows ($f_1$ and $f_2$) and volumes ($v_1$ and $v_2$) in each component are related to their mean circulation times ($t_1$ and $t_2$) by the formula

$$\frac{t_2}{t_1} = \frac{\frac{f_1}{v_1}}{\frac{f_2}{v_2}} \qquad (1)$$

by substitution, the ratio of the flows

$$\frac{f_2}{f_1} = \frac{T - t_1}{t_2 - T} \qquad (2)$$

can be derived ($T$ is mean circulation time of the total curve) without determining absolute flow. The ratios of the volumes are determined by the formula

$$\frac{v_2}{v_1} = \frac{f_2}{f_1} \times \frac{t_2}{t_1}.$$

In normal subjects the average ratios for forearm and hand, forearm alone, and hand alone were similar: $f_1$ averaged 9 times $f_2$ and $v_1$ 4 times $v_2$. During venous congestion $f_1$ was twice $f_2$ and $v_1$ one-half $v_2$. In congestive failure $f_1$ averaged twice $f_2$; $v_1$ one-third $v_2$. Washout (virtual disappearance) times averaged 7 minutes in normals, 1 minute in vasodilated subjects, 15 in venous congestion and 19 minutes in congestive failure.

The upper extremity blood flow, except under conditions of maximum vasodilatation, is multiphasic usually resolvable into two components of greater and lesser velocities. In the normal subject, flow and volume are considerably greater in the rapid portions. Preliminary results in congestive failure suggest that flow and especially volume of the slow components, relative to the fast components, are greatly increased.

**An Analysis of the Clinical Response and Tolerance of the Elderly Cardiac to Various Digitalis Preparations**

*R. E. Fremont, New York, N. Y.*

While the experimental pharmacologic differences of various digitalis preparations are well proven, the clinical documentation does not appear adequate. Also, the frequency with which cardiac and extracardiac factors alter the response to digitalis and lead to unjustified incrimination of digitalis is not sufficiently appreciated. Thus, both underdigitalization and overdigitalization with toxicity occur more often than necessary, particularly, in elderly patients.

An attempt was made, therefore, to analyze the clinical response and tolerance of all cardiac patients over 60 years of age treated at the Brooklyn Veterans Administration Hospital with various digitalis drugs from 1951 to 1954. This involved 150 patients with 259 periods of observation on leaf, digitoxin, digoxin, gitaligen, cedilanid, and sublingual digitoxin. The factors evaluated were age, etiology, degree of cardiac failure, cardiac rhythm, state of the myocardium in terms of ischemia and irritability, renal function, gastrointestinal and pulmonary factors, and electrolyte balance, type of digitalis and mode of administration. These factors were related to the incidence, degree, manifestations and duration of toxicity. The clinical response was difficult to evaluate due to the variety of therapeutic agents used.

In evaluation of toxicity, the following was found: (1) advancing age proved of only suggestive significance; (2) arteriosclerotic and hypertensive cardiacs exhibited toxicity more frequently than those with the rheumatic heart disease and this

occurred more often with leaf than with digoxin or digitoxin. However, figures on complete tolerance favor leaf and digoxin.

Further analysis revealed (1) the insignificant role of the degree of cardiac failure, (2) the important effect of advanced myocardial ischemia in predisposing to toxicity, particularly of a cardiac nature. In spite of the prevalence of this factor there was better tolerance of digoxin than of digitoxin or leaf. Myocardial ischemia, however, frequently simulated toxicity and led to underdigitalization. Gastrointestinal symptoms occurred with digoxin as often as with digitoxin and leaf and proved unrelated to concomitant gastrointestinal disease. The latter often simulated digitalis toxicity. Renal insufficiency was rare, but there was better tolerance of digoxin than digitoxin. Electrolyte imbalance was not encountered probably because of adequate prevention. Pulmonary complications accounted for toxicity, regardless of the preparation, because of mistaken resort to excessive doses. Initial digitalization led to toxicity even with digoxin but severe myocardial ischemia was a particularly common predisposing factor, as was myocardial irritability. Maintenance therapy was associated with toxicity when non-recognition of predisposing factors or complications led to excessive dosage. Cedilanid was well tolerated when used for rapid digitalization. Gitaligen proved disappointing except in a rare case of marked myocardial irritability and severe failure. Sublingual digitoxin proved valuable in patients with marked gastrointestinal intolerance.

**Persistent Problems in the Diagnosis and Treatment of Bacterial Endocarditis**

*Charles K. Friedberg and Robert C. Taymor, New York, N. Y.*

Serious problems arise and avoidable errors still occur in the diagnosis and treatment of bacterial endocarditis. The diagnosis is occasionally discovered only at autopsy and it is frequently delayed until serious damage or an irreversible complication has occurred. Death may occur despite apparent bacteriologic cure, or else a cure is effected after unnecessarily prolonged morbidity and expense. When the diagnosis is made, frequent problems arise as to choice of therapy, indications for change and the interpretation of need for retreatment with supposed relapse. This presentation classifies specific examples from actual cases, many of these problems have occurred in hospital and consultation practice. The specific problem or error is indicated in each instance with recommendations about procedure.

Problems or errors in diagnosis arose in connection with: (1) fever without localizing symptoms; (2) fever with misleading localization; (3) fever without apparent cardiac murmur; (4) cardiac murmur with afebrile or subfebrile course; (5) cases with persistently negative blood cultures. A similar classification is presented, with individual examples, of cases in which bacterial endocarditis was diagnosed, though absent. These errors may be avoided by close adherence to diagnostic criteria which are defined.

Problems or errors in therapy are discussed with specific case examples under the headings: (1) initiation of treatment before a positive blood culture is obtained, and management in cases with persistently negative blood cultures; (2) management in cases with positive blood cultures in which sensitivity studies are absent or inaccurate; (3) management in cases in which *streptococcus viridans* and *streptococcus fecalis* are not clearly distinguished; (4) deceptive remission followed by relapse in combined therapy including broad spectrum antibiotics; (5) improper and unnecessary changes in treatment because of transient or persistent fever; (6) improper changes in therapy due to petechiae or emboli and (7) cases due to resistant *streptococcus fecalis* or *micrococci*.

**Experimental and Clinical Study of the Effect of Beta Sitosterol Administration on Intestinal Absorption of Dietary Cholesterol and the Plasma Cholesterol Content of Patients with Coronary Artery Disease**

*Meyer Friedman, Richard Homer and Sanford O. Byers, San Francisco, Calif.*

If plasma is exposed to an ether alcohol solution, a fraction of its cholesterol content wil be dissolved in the latter. The fraction thus dissolved is termed the easily extractable portion of plasma cholesterol. The size of this fraction in earlier studies has been found to be dependent upon the ingestion of dietary derived cholesterol, i.e. its size may be employed as an indicator of the degree of intestinal absorption of cholesterol. Employing this test, the effect of the administration of sitosterol upon the intestinal absorption of a standard dose of cholesterol was studied in six patients suffering from coronary artery disease. Intestinal absorption of dietary cholesterol was determined in rats by direct analyses of intestinal lymph. Plasma cholesterol studies also were obtained upon these same patients at various time intervals during a 6-month-period of sitosterol administration.

Our results indicate that sitosterol administration had no significant effect upon the intestinal absorption of cholesterol either in the patients as determined by the extraction test or in rats by direct measurement of intestinal cholesterol. Furthermore, the changes in the plasma cholesterol concentration of the 6 patients after 6 months of continuous oral ingestion of cholesterol were considered insignificant.

**Salt and Water Balance in Experimental Hypertension**

*Sydney M. Friedman and Constance L. Friedman, Vancouver, British Columbia, Canada*

Salt and water handling was studied in a variety of representative types of experimental hypertension in the rat. The forms of hypertension studied were (1) active DCA, (2) sustained post-DCA (metacorticoid), (3) Compound F, (4) renal compression and (5) spontaneous hypertension of age. Tolerance to salt and water was examined both with and without loading and with and without Pitressin treatment. The role of the kidney was explored with clearance tests where necessary.

A common pattern of derangement, centered around an acceleration in the rate of elimination of water and Na, occurs in all of the above forms of hypertensive disease and seems related to similar aberrations noted in man. The kidney is involved because of its special central role in salt and water homeostasis. The data suggest that the observed phenomena are at least partially related to posterior pituitary dysfunction.

**Resection of the Aortic Arch Using Vessel Couples**

*James D. Fryfogle and John T. Small, Detroit, Mich.*

The accepted method of vessel anastomosis requires intima to intima approximation by suture. Unfortunately, all modifications of such technic are time consuming and necessitate an interruption of the flow of blood for their performance. In resecting blood vessels that lead to vital viscera, i.e. branches of the thoracic and abdominal aortas, these viscera suffer from prolonged deprivation of oxygenated blood. We have devised and utilized, experimentally, a method by which rapid insertion and restoration of normal blood flow are accomplished, with an intima to intima suture method then being performed at leisure. A simple ingenious prosthesis is employed and is bivalved to effect its removal. The ultimate aim of the vascular surgeon is the successful resection of the aortic arch. Acute and long-term studies in 23 experimental animals demonstrated the acceptability of this method in aortic arch resection. Blood flow to the brain can be re-established in under 5 minutes.

**The Importance and Evaluation of Certain Non-Pathologic Factors which Produce Changes in Electrocardiograms**

*Manuel Gardberg and Irving Rosen, New Orleans, La.*

It is impossible to recognize the abnormal unless one knows the full range of changes which may occur under normal conditions. This principle must be applied to the reading of the routine interval ECG as well as to ECGs made after exercise and employed as a test for coronary disease.

Following this principle one of us decided to investigate the effect on the ECG of certain daily activities. A report on the effects of taking food was made in 1938. Recently, controlled studies on the effect of food, of exercise and the combined effect of food and exercise have been made in a group of normal young adults.

All previous reports on the effect of exercise and of food, including the 1938 report, draw conclusions entirely on an empiric basis. Our study demonstrates that the effects produced by these factors are not without order, but demonstrates that the changes are due to a decrease in magnitude of the ventricular gradient without a change in its direction. The varying T wave changes, due to these factors in different individuals, are thus easily explainable, even predictable, by this knowledge and consideration of an individual's QRS axis.

A simple method of employing the principle involved in the clinical interpretation of the ECG, as well as a number of examples, are furnished. Its employment will avoid serious errors in interpreting routine and exercise tracings.

**Angiocardiographic Diagnosis of the Cyanotic Types of Congenital Malformations of the Heart: An Eight Year Study of 218 Patients**

*B. M. Gasul, E. H. Fell, G. Hait, R. F. Dillon, C. J. Marienfeld and H. G. Bucheleres, Chicago, Ill.*

During the past eight years about 450 separate angiocardiograms, each consisting of from 15 to 25 films, have been reviewed for this study. A Fairchild camera with serial roentgenograms at one-half second intervals, and exposures at one-thirtieth to one-sixtieth of a second was used. In this series of cases, no death occurred directly attributable to the procedure. A complete physical, fluoroscopic, roentgenologic and ECG study was done on all 218 patients before an angiocardiogram was taken. In addition to these examinations, the authors further confirmed the diagnosis in 110 patients by means of catheterization of the heart and of the great vessels, in 76 patients by surgery, and in 61 by autopsy findings. The vast majority of our patients are infants and children.

Illustrative angiocardiographic films are used to demonstrate the salient points in the diagnosis and differential diagnosis of 21 cyanotic types of congenital malformations of the heart, which we encountered in our studies. Tables summarize the number and age of patients studied for each entity as well as the important points in the angiocardiographic diagnosis and differential diagnosis of these various entities.

Our own interpretations of our angiocardiograms have been constantly changing in the light of a correlative clinical, roentgenologic, ECG, catheterization, surgical and post mortem findings. We now feel, on the basis of all these findings, that (1) the diagnoses of tetralogy of Fallot, complete transposition of the great vessels and anomalous entrance of the pulmonary veins into the great systemic veins can almost always be made from a properly per-

formed and properly interpreted angiocardiogram; (2) the diagnosis of Taussig-Bing heart, truncus communis arteriosus, tricuspid atresia and pulmonary stenosis with interatrial communication can usually be made from a properly performed and properly interpreted angiocardiogram; and (3) all other forms of the cyanotic types of congenital malformations of the heart require additional studies before a definite diagnosis can be established.

**Cardiospectrograms**

*George D. Geckeler, William Likoff and Daniel Mason, Philadelphia, Pa.*

A spectrum analysis measures the energy distribution of a physical event and records it as a function of time and frequency. The present investigation has applied this advance in electronics to the study of heart sounds. The records obtained have been identified as cardiospectrograms.

The equipment used to record heart sounds consisted of either a Brush contact or a Western Electric 618A microphone, modified with a rubber seal, a low noise preamplifier and an Ampex Model 300 magnetic tape recorder. The recordings were cut and spliced into continuous loops of three and one-half seconds duration. They were made at 15 inches per second, increased in speed 4 times and were transcribed into spectrograms by courtesy of the Bell Telephone Laboratories. All of the cardiospectrograms display frequency of sound along the vertical axis, time along the horizontal axis and intensity by the darkness of the pattern.

Cardiospectrograms, though in the preliminary phase of development have clarified certain features of normal and abnormal sounds and murmurs. Portrayals of normal first sounds indicate wide variations in which low frequencies and increased duration do not always predominate over normal second sounds. The patterns of the audible third heart sounds are distinct and permit the differentiation between gallop rhythm, the opening snap of mitral stenosis, and a systolic click. The sharp first sound of mitral stenosis is not louder than normal, but is shorter in duration and higher in pitch. Although it is difficult to predetermine the value of cardiospectrograms, they may prove of help in determining the genesis of sounds and murmurs, an aid in teaching auscultation, serve as an important clinical tool in differentiating obscure auscultatory events and also serve in carrying out mass screening programs.

**Silent Electrocardiograms in the Presence of Myocardial Infarction: A Comparison with the Spatial Vectorcardiogram**

*David Gelfand and Samuel Bellet, Philadelphia, Pa.*

Myocardial infarction of sufficient magnitude to alter the normal orientation of the initial forces of accession will give rise to a significant Q wave in one or more of the leads of a standard 12-lead ECG. If a myocardial infarct is anatomically located in the postero-basal (high posterior) wall of the left ventricle, the altered initial forces of accession are oriented primarily anteriorly, at times slightly to the right, either slightly superiorly or inferiorly. Such an orientation fails to inscribe significant Q waves in the standard limb, unipolar limb and unipolar precordial leads. Such an ECG could be interpreted as being within normal limits. The spatial vectorcardiogram (using tetrahedron and cube co-ordinates) in such patients shows a characteristic alteration of the form (rounded instead of oval), orientation (initial forces markedly anterior for at least 0.04 second), and/or direction of rotation (clockwise rotation in the horizontal plane) of the QRSsÊ loop. Examples of seven such cases, acute, sub-acute and healed are shown with serial ECGs, spatial vectorcardiograms and correlated with necropsy findings. It is concluded that the spatial vectorcardiogram may be helpful in the diagnosis of myocardial infarction located in the postero-basal wall of the left ventricle in the presence of a "silent" ECG.

**The Double A Wave of the Jugular Pulse**

*David Gelfand, Philadelphia, Pa.*

The A wave of the jugular pulse is dependent upon right atrial contraction with changes in volume, pressure and velocity in the jugular vein. In the presence of an interatrial septal defect, the shunt of blood from the left to the right atrium causes a double A wave to appear on the phlebogram. The Valsalva maneuver, by increasing the pressure in the right atrium, reduces the left-to-right shunt of blood and the double A wave is replaced by a single, tall A wave. In 9 patients, diagnosed as having congenital interatrial septal defect by clinical examination, roentgen examination, angiocardiography, cardiac catheterization and cardiac surgery, a double A wave was recorded in the phlebogram. Tracings of the jugular pulse simultaneously recorded with ECGs, phonocardiograms, cardiograms and intra-atrial (right) pressure curves will be shown. It is concluded that the phlebogram, a simple non-traumatic diagnostic procedure, is helpful in the diagnosis of interatrial septal defect, when there is co-ordinated atrial contraction with a left-to-right shunt of blood between the atria.

**The Mechanism of Cardiac Changes Observed in Uremia**

*M. M. Gertler, J. Kream and J. W. Hylin, New York, N. Y.*

The concomitant and sequential cardiac changes in the early and terminal stages of uremia as manifested by the ECG closely parallel the cardiac changes often observed with high levels of serum potassium and/or stimulation of the cardiac branches of the vagus. These changes cannot be

attributed solely to changes in intracardiac serum electrolytes for the relationship between intracardiac electrolytes and ECG measurements has not been firmly established. Because of the known association between vagal stimulation and potassium concentration, another possible mechanism for these changes in uremia was considered, namely, a study of the cholinesterase system in cardiac musculature.

Uremia was produced in 8 male dogs by bilateral ligation of the ureters. Three animals were treated actively with ionic exchange resins while 5 were permitted to continue the usual uremic course. ECGs were taken daily on the animals and when death appeared imminent, the animals were sacrificed. The hearts were quickly removed and frozen. Homogenates of ventricular muscle were made and analysis were performed for cholinesterase activity by Ammon's method.

It was found that the uremic animals had an average cholinesterase activity of 2.8 units (range 2.1 to 3.3) while in the normal animals the average was 4.4 units (range 3.5 to 5.6) as indicated by $QCO_2$ values. The significance of these findings as a possible explanation for the cardiac changes observed in uremia are discussed.

**Serum Transminase Levels in Experimental Pulmonary Infarction and Pericarditis**

*H. F. Glassner, H. I. Jacobs and C. M. Agress, Los Angeles, Calif.*

Serum glutamic oxalacetic transaminase (SGO-T) measurements have been shown to be useful in the diagnosis of acute myocardial infarction on the basis of both experimental and clinical studies. Since the diagnosis of many clinical cases of myocardial infarction is often complicated by equivocal ECG findings, the present work was undertaken to examine the SGO-T levels of dogs with experimental pulmonary infarction and pericarditis.

Pulmonary infarction was produced in 9 dogs by a modification of the technic reported by Chapman and his co-workers. Three dogs were used as controls. Serum samples were taken at intervals of approximately 2, 15, 20 and 40 hours post injury. At autopsy all organs were examined and the area of the lung, which had undergone infarction, was estimated. Color photographs were taken of all lungs. Pulmonary infarction involved from 5 to 45 per cent of the total lung. Pericarditis was produced in 8 dogs. The chest was opened and either sterile talc, sand or α streptococci were inserted in the pericardial sac. The chest was closed and the animals returned to their quarters. Three dogs were used as controls. Serum samples and ECGs were taken at approximately 24-hour intervals post injury for 5 days. At autopsy all organs were examined. Serum samples of both groups were analyzed for SGO-T levels.

The results indicate that neither experimental pulmonary infarction nor experimental pericarditis produce significant rises in SGO-T levels. The slight rises which did occur in those dogs with experimental pericarditis could be attributed to the acute epicardial inflammation produced by the inflammatory agents. Further there was no correlation between the SGO-T levels observed and the severity of the experimental lesions. This study suggests that SGO-T levels may possibly be clinically useful in distinguishing between myocardial infarction and either pulmonary infarction or pericarditis.

**The Surgical Treatment of Mitral Insufficiency by Total Circumferential Suture of the Mitral Ring (Mitral Purse-String)**

*Robert P. Glover, J. C. Davila, R. G. Trout and N. Wood, Philadelphia, Pa.*

Heretofore, methods for the correction of mitral insufficiency have almost exclusively employed the introduction of foreign material within the lumen of the cardiac chambers for the purpose of adding substance to the deficient valve tissues. These methods were utilized, despite the fact that little or no experimental data was obtained or published prior to clinical application. The fact that these methods have failed to accomplish the designed purpose, therefore, is not surprising.

A new concept for the correction of mitral valve insufficiency as seen clinically and experimentally is herein reported. This concept takes into account that in addition to the absolute loss of valve tissue seen in such contracted valves, in many instances there is also a relative loss of valve tissue, occasioned by dilatation of the mitral ring. The proper application of a circumferential suture of suitable material, appropriately constricting the atrioventricular mitral ring, reduces the size of the mitral lumen to be occluded, relieves the tension of the mitral valve leaflets and their taut and deformed chordae tendineae and allows the valve leaflets to co-apt without the introduction of foreign material into the left heart chambers.

Three years of experimental investigation have preceded the present clinical application of mitral purse-string. During this time, 25 cadavers and 150 dogs have been used for anatomic, pathologic and physiologic study. The results of these studies have been published elsewhere.

The first 12 clinical cases of mitral insufficiency, treated by total circumferential suture of the mitral ring, are presented. The results obtained are demonstrated by radiography, ECG, phonocardiography, and hemodynamically by pressures taken within the left atrium and by clinical evaluation. Actual valve action in insufficiency and as corrected by "mitral purse-string" are demonstrated.

### Observations on the Use of Radioactive Iodine in Paroxysmal Tachycardia

*Herbert Gold, Eliot Corday and Henry L. Jaffee, Los Angeles, Calif.*

During the past 3 years, the authors have treated euthyroid patients with paroxsymal atrial tachycardia and atrial fibrillation with rapid ventricular rates with radioactive iodine. These patients had coronary artery disease as designated by history, physical examination, ECG changes and/or a positive Master two-step test. When most of these patients experienced paroxysmal tachycardia, they noted very severe precordial distress.

Treatment with radioactive iodine dramatically reduced the number of paroxysms of tachycardia. In 6 patients, when the paroxysmal tachycardia occurred subsequent to $I^{131}$ treatment, the patients no longer experienced the previous precordial distress. Two of the patients were not even aware that they were having episodes of tachycardia.

Several reports suggested that radioactive iodine reduced anginal pain in the euthyroid cardiac patient by reducing the work load of the heart. As a result of our study, we propose to show that the work load of the heart was not reduced in the patients who experienced recurrence of paroxsymal atrial tachycardia following $I^{131}$ treatment. The ventricular rates were often faster than previously noted, prior to the treatment and, therefore, the work load of the heart could not have been lessened. As a result of this study, it is suggested that anginal pain in the euthyroid coronary patient is reduced because of some metabolic change in the myocardium following treatment with $I^{131}$.

### Simultaneous Catheterization of the Left and Right Sides of the Heart

*Harry Goldberg, Janet Dickens, Edward Hayes and George Raber, Philadelphia, Pa.*

Simultaneous catheterization of the right and left heart allows for recording pressures from all chambers and estimation of cardiac output. Right heart catheterization is performed with the patient in the prone position. A 6 inch no. 18 needle is introduced into the left atrium paravertebrally. A polyethylene or polyvinyl catheter is passed through the needle and into the left ventricle and occasionally into the aorta. Pressure gradients across the mitral and aortic valves may thus be obtained. When it is not possible to enter the aorta, the brachial arterial pressure may be substituted for the aortic pressure with reasonable accuracy. Simultaneous recording of the pressure gradients and flow by direct Fick method across stenotic orifices, allows for a more accurate estimate of ventricular work and orifice size, particularly in aortic stenosis. This procedure was performed 24 times in 21 patients; 6 had pure mitral stenosis, 10, pure aortic stenosis, 4, multivalvular lesions and 1, mitral regurgitation. There were no mortalities in this group.

In mitral stenosis the cardiac index was low (1.1 to 2.5 L. per minute per M.$^2$). The left atrial pressures were elevated (11 to 39 mm. Hg). These compared favorably with the pulmonary capillary pressures recorded simultaneously. The left atrial–left ventricular diastolic pressure gradients were constantly observed (11 to 17 mm. Hg). Right ventricular work was generally increased (0.7 to 2.2 Kg. per minute per M.$^2$). The effective left ventricular work was normal or decreased (1.26 to 3.02 Kg. per minute per M.$^2$). The mitral valve areas were markedly reduced (0.46 to 1.1 cm.$^2$).

In aortic stenosis the cardiac output was generally low (1.0 to 2.7 L. per minute per M.$^2$). The left ventricular-aortic (or brachial arterial) systolic pressure gradients were appreciable (35 to 118 mm. Hg). The total left ventricular work was increased (2.41 to 6.01 Kg. per minute per M.$^2$). The aortic valve areas were markedly reduced (0.15 to 0.94 cm.$^2$).

The procedure was repeated in 3 patients, following aortic commissurotomy. The left ventricular–brachial arterial mean pressure gradient fell appreciably in 2 patients and minimally in the third. The cardiac output increased in 2 and was unchanged in 1, the aortic orifice was increased in 2 and remained unaltered in 1. Simultaneous catheterization of the right and left heart is not only valuable in assessing the total dynamics in aortic and mitral valvular disease, but also in evaluating surgical technics for correction of lesions affecting these valves.

### Cardiopericardiomyopexy in the Treatment of Rheumatic Heart Disease

*Aaron N. Gorelik, New York, N. Y.*

A group of patients, incapacitated because of rheumatic valvular heart disease, have been rehabilitated by cardiopericardiomyopexy.

There were 50 cases of advanced mitral stenosis with varying degrees of mitral insufficiency. Of these cases, 9 had tricuspid valve involvement, 5 pure mitral stenosis, 3 advanced aortic stenosis and insufficiency associated with mitral stenosis, 4 pure mitral insufficiency, 5 atrial fibrillation. The majority of the patients presented moderate to severe degrees of chronic recurrent congestive failure, with chronically enlarged liver, pulmonary congestion and peripheral edema.

Cardiopericardiomyopexy converts an ischemic to an hyperemic myocardium by the introduction of magnesium silicate U.S.P. talc powder into the pericardial sac and by uniting the pectoral muscle to the pericardium. The talc produces an acute foreign body inflammatory reaction which opens up intercoronary channels, increases the number of the

*telae arteriae adiposae* and produces a generalized granulomatous adhesive pericarditis. The union of the pectoral muscle to the pericardium produces vascular adhesions between the muscle and the pericardium.

Autopsies revealed definite collateral vascular formation in a generalized adhesive granulomatous pericarditis and between the pectoral muscle and the pericardium. The pericarditis or foreign body inflammation persists for a very long time, without interfering with the patient's daily activities.

According to Karsner, Bayliss, Gross and Klemperer, the pathology of the myocardium of rheumatic patients shows various degrees of narrowing of the lumen of the coronary arteries and their branches, thus simulating arteriosclerosis with the resulting ischemia of the myocardium.

Having revascularized the myocardium in patients with coronary arterial disease with satisfactory results, it was thought that cardiopericardiomyopexy will revascularize the myocardium of the rheumatic myocardium and thus will improve the function and strengthen the myocardium so that it could withstand the mechanical effect of the valvular stenosis or insufficiency or further valvular surgery, if necessary.

**A Simple Test for Detecting the Altered Cardiodynamics of Ventricular Failure or Mitral Stenosis**

*Richard Gorlin and John H. Knowles, Portsmouth, Va.*

In the presence of heart failure or mitral stenosis, a characteristic arterial pressure response occurs during the Valsalva maneuver which is markedly different from the normal. Studies of circulatory function were made in 65 patients, and on 20 of these, cardiac catheterization were performed. The normal response, rapidly falling arterial pressure on straining, was associated with simultaneously decreasing pulmonary capillary pressure; this was seen in normal subjects, in pregnancy and in cardiacs without failure (class I cardiacs). The abnormal response, sustained arterial pressure on straining, was associated with unchanged right atrial or pulmonary capillary pressure; this was seen only in patients with severe right or left ventricular failure or tight mitral stenosis (class III or IV cardiacs).

The difference between a normal and an abnormal response was shown to depend on a flattened right or left ventricular function curve or a flattened mitral valve pressure-flow curve. Diagnosis of left ventricular failure was considered valid only in the absence of severe right ventricular failure. Because of these strikingly abnormal findings in disease and their obvious significance, a clinical test was devised utilizing auscultatory sphygmomanometry to detect the pressure response. The test was applicable in the differential diagnosis of dyspnea, in the diagnosis of minimal left ventricular failure or mitral stenosis and, particularly, in the detection of the effects of therapy in disease. Changes in position affect the response. This was particularly useful in eliciting and quantitating borderline abnormalities of cardiac function.

**Chronic Isolated Rheumatic Auriculitis Associated with Mitral Stenosis: Its Possible Relation to Atrial Fibrillation, Mural Thrombosis and Embolism**

*Irving Graef and O. Alan Rose, New York, N. Y.*

Biopsies of atrial appendages removed during mitral commissurotomy have provided unexpected evidence that active rheumatic tissue changes may be found in this site in patients with mitral stenosis, even in the absence of clinical evidence of active rheumatic fever. It is not widely appreciated that these findings may be limited to the left atrium and its appendages; this may play a significant role in the occurrence of atrial thrombosis and supraventricular arrhythmias.

We have studied 3 subjects with advanced mitral stenosis whose clinical courses were characterized by atrial fibrillation, congestive heart failure and repeated embolization, culminating in death at the ages of 38, 50 and 57 years, respectively.

At necropsy each presented severe mitral stenosis and lesions of recent and old rheumatic inflammation, confined to the left atrium. The changes included typical endocardial palisading subjacent to fresh or organizing thrombi. In 2 the thrombi were minute, in the third a thrombus nearly filled the auricle. In all, sections of the auricle contained laminas of Aschoff cells lying in the swollen endocardium or subendocardium or clustered in the adjacent myocardium. No active lesions were found elsewhere in these hearts, although healed valvular and myocardial lesions were abundant.

It seems probable that the clinical course may be influenced by such atrial lesions, particularly in the occurrence of thromboembolism and supraventricular arrhythmias.

These and earlier reported observations suggest a direct relationship between the obstructive factor of mitral stenosis and the persistence of atrial rheumatic activity. If the relief of mitral stenosis reduces the tendency to persistent auriculitis and its consequences, then commissurotomy may have more than hemodynamic value.

**Responsiveness of Vasomotor Receptors in the Major Vascular Beds**

*Harold D. Green and Adam B. Denison, Winston-Salem, N. C.*

Pressure and flow (electromagnetic meter) were measured in appropriate arteries in anesthetized

dogs during intra-arterial injections and nerve stimulations. Arterenol (norepinephrine) and methylarterenol (epinephrine) caused vasoconstriction in all but the coronary artery; secondary vasodilation was prominent after methylarterenol. Progressively increasing doses of adrenergic blocking drugs (1) converted the responses to methylarterenol to vasodilation in skeletal muscle, mesenteric and cerebral beds; (2) abolished the remaining constrictor responses to methylarterenol and arterenol and (3) finally abolished the dilator responses to methylarterenol. Isopropylarterenol (isopropylnorepinephrine) induced vasodilator responses similar to those elicited by methylarterenol during partial adrenergic blockade; these were abolished by the same doses of the adrenergic blocking drugs. All 3 adrenergic substances caused mild coronary vasodilation and myocardial stimulation. Intra-arterial methacholine caused moderate vasodilation in skeletal muscle and the cerebral bed but not in the skin.

Adrenergic (sympathetic) nerve stimulations, identified by blockade with adrenergic blocking drugs, caused only vasoconstriction, practically identical with that of arterenol. Cholinergic (parasympathetic) nerve stimulation, identified by blockade with atropine, induced vasodilator responses only in skeletal muscle. Reactive hyperemia was recorded in the myocardial, skeletal muscular and renal vascular beds, and inconsistently in the mesenteric bed, but not in cerebral and cutaneous beds.

The vasomotor receptors include (1) adrenergic constrictor receptors which are innervated (mediator arterenol) and are responsive to the hormones arterenol and methylarterenol (epinephrine); (2) adrenergic dilator receptors which are non-innervated but are sensitive to methylarterenol and isopropylarterenol; (3) cholinergic dilator receptors which are innervated and (4) non-innervated dilator receptors which are sensitive to the local tissue metabolic needs. The adrenergic constrictor receptors are present in all beds except the coronary but are relatively less effective in the cerebral than in the other beds; the adrenergic vasodilator receptors are highly effective in skeletal muscle, moderately effective in the mesenteric bed and slightly effective in the coronary, cerebral and cutaneous beds but apparently absent in the renal bed; methylarterenol (epinephrine) acts as if it were a mixture of approximately equal parts of arterenol and isopropylarterenol.

In instances of impaired myocardial or cerebral blood flow due to arterial hypotension, widespread sympathetic vasoconstrictor nerve activity or infusion of arterenol would appear to be greatly superior to infusion of methylarterenol (epinephrine) because of the much smaller secondary dilation. The cardiovascular significance of the dual (dilator-constrictor) activity of the adrenal hormone methylarterenol (epinephrine) remains obscure.

**Left Atrial Pulse Pressure in Mitral Valvular Disease**

*David G. Greene, Ivan L. Bunnell, John T. Sharp and Joseph E. Macmanus, Buffalo, N. Y.*

One of the prominent questions involved in the surgical therapy of mitral valvular disease is that of the relative degree of mitral stenosis and mitral insufficiency. Although left atrial pressures in experimental lesions in animals have been shown to differ in stenosis and insufficiency, reports of measurements in human subjects have been conflicting.

The present series of measurements were made in 32 patients with rheumatic heart disease subjected to thoracotomy for exploration of their mitral valves. The pressures were obtained through a short 22 gage needle attached to an inductance gage which was sterilized and introduced directly into the chest cavity. A Hathaway blood pressure recording system was used. The pulse pressures in the left atrium were measured from the photographic records. In 4 patients with free mitral insufficiency, pulse pressure in the left atrium was between 22 and 39 mm. Hg. Stenosis in these patients was present to only a minor degree. In 21 patients with pure mitral stenosis and no evidence of mitral insufficiency, the pulse pressure was between 4 and 19 mm. Hg. In 7 patients with mitral stenosis, which was the significant lesion hemodynamically, but who also had a regurgitant jet through the mitral valve appreciable to the palpating finger of the surgeon, the left atrial pulse pressure was between 4 and 21 mm. Hg.

From these findings it appeared that a pulse pressure over 22 mm. Hg. was correlated with a high degree of mitral insufficiency. Others have shown that severe degrees of mitral insufficiency are incompatible with severe mitral stenosis. A wide pulse pressure in the left atrium, therefore, indicates the absence of severe mitral stenosis. Pressures obtained directly at surgery have been correlated with pressures obtained by direct puncture through the back and by wedge position of the catheter in the pulmonary artery at cardiac catheterization.

**Tissue Metal Concentrations: A New Dimension in Medical Investigation**

*George C. Griffith and Edward M. Butt, Los Angeles, Calif.*

The metallic content of cardiovascular and related structures has been studied in the laboratories of the University of Southern California since 1949 by means of the emission spectroscope. Our purpose has been (1) the establishment of tables of norms for each metal in the various tissues of the body; (2) the determinations or patterns of distribution of these elements in normal systems, preliminary to the identification and investigation of deviant patterns occurring in disease states; (3) investiga-

tion into the role of metals in the pathophysiology of such deviant states and (4) the study of the fate of metallic compounds administered therapeutically to our patients.

Concurrently with our studies, investigators both in this country and abroad have turned their efforts to study of metal-enzyme relationships. Others have concentrated on the use of serum metal determinations in differential diagnoses and have discovered, for example, that levels of serum iron and copper serve to distinguish between infectious hepatitis and obstructive jaundice. Still others have examined the close parallel between stresses, such as myocardial infarction or trauma, and levels of metals in the blood stream, observing that a sharp drop in the concentration of a certain metal precedes and predicts the future onset of complications or discomfort.

Minute quantities of metals exert a profound metabolic effect due to their interaction with enzymes, hormones and vitamins or as a result of their deficiency, toxicity or imbalance. This makes understanding the role of metals in the body economy basic to the identification, prognosis and treatment of disease in its first stages. The biologic assay furnishes an earlier and more exact index of health and disease than is furnished by slide and microscope.

**Digitoxin and Uncoupling of Oxidative Phosphorylation**

*Santiago Grisolia, Kansas City, Kan.*

Concentrations of 3.35 to 6.7 by $10^{-5}$ M digitoxin which have little effect per se upon respiration or P/O ratios of mitochondrial preparations. They show a marked potentiating effect upon uncoupling by 2,4-dinitrophenol (DNP). The potentiating effect has been shown with concentrations of 1.25 to 5 $\times$ $10^{-5}$M of DNP. For example, the following values were obtained with 1.8 mg. mitochondrial nitrogen 100 $\mu$M of glucose and enough hexokinase to transfer 30 $\mu$M of ATP per minute: Control, 7.85 microatoms oxygen, P/O 2.18; with 1.25 $\times$ $10^{-5}$M DNP, 7.45 microatoms oxygen, P/O 2.25; with 3.35 $\times$ $10^{-5}$M digitoxin, 8.9 microatoms oxygen, P/O 2.16; with digitoxin and DNP, 9.25 microatoms oxygen, P/O 1.7. Incubation for 15 minutes at 38 C. with the following substrates in $\mu$M per 2 ml.: potassium phosphate, 30; tris (hydroxymethyl) aminomethane buffer pH 7.4, 100; potassium glutamate, 36; potassium ATP, 4; cytochrome C .027; magnesium ions, 15 and sucrose to bring the medium to isotonicity.

The uncoupling is markedly affected by the inorganic composition of the medium and the pH. Respiration is affected, although not as markedly. For example, substitution of Na for K results in P/O ratios of 0.5 and lower, with a decrease in respiration of near 50 per cent. When DNP is replaced by triiodothyronine (TIT) in concentrations 3 times higher than DNP, the effect is not as clear and depends markedly on the concentrations of both TIT and digitoxin. This is not surprising however, since TIT might uncouple phosphorylation, presumably by swelling the mitochondria. Although up to now this work has been done with guinea pig liver mitochondria and digitoxin, a comparative study with mitochondria from other tissues and with other compounds related to digitoxin will be presented.

These preliminary experiments tentatively indicate that digitoxin acts on the permeability of mitochondria. To the knowledge of the author, this is the first demonstration of a metabolic action of digitoxin at a subcellular level.

**Graphic Recording of Heart Sounds and Vibrations by a New Electronic Pickup**

*Dale Groom and John A. Boone, Charleston, S. C.*

The vibrational energy produced at the chest wall by the heart beat is a direct function of the mechanical activity of the heart as a pump. Only a relatively small portion of this energy can be appreciated by the human ear as sounds; the remainder lies in a range of low, infrasonic frequencies to which conventional phonocardiographic microphone pickups, as well as the ear, are insensitive.

A new type of electronic pickup has been developed in collaboration with the General Motors Research Laboratories for use in direct contact with the precordium in the graphic recording of heart sounds and vibrations. It is a displacement type of pickup, designed particularly for reproduction of the low, subaudible frequencies, and utilizes the RCA 5734 transducer tube to transform mechanical motion into electric potentials which may be recorded on conventional oscillographic equipment. Calibration of the pickup has shown that it is capable of reproducing the wave forms of mechanical vibrations, with a high degree of fidelity, over its useful frequency range of 2 to 500 c.p.s. Studies of the cardiac vibrational pattern in normal subjects indicate that the precordium is in virtually constant motion throughout the heart cycle. The frequency spectrum of this motion may be divided into three main categories:

(1) The cyclic movements of inward and outward excursion of the chest wall are of a comparatively gross nature and correspond to what was designated many years ago as the "cardiogram." (2) Infrasonic vibrations, low frequency oscillations extending from perhaps 2 c.p.s. on up to the lower limit of auscultatory audibility; containing a major portion of the total cardiac vibrational energy transmitted to the body surface, their wave forms are selectively distributed over the precor-

dium somewhat as heart sounds are and tend to extend throughout the cardiac cycle; since this is the frequency range of the ballistocardiogram (BCG) a recording of them constitutes, essentially, a precordial BCG. (3) Audible vibrations, the heart sounds and murmurs heard on auscultation; examination of wave forms of these sounds reveals a basically "noise" type of pattern, a few murmurs of musical quality showing prominent sinusoidal characteristics.

In general, the amplitude of precordial motions increases as their frequency decreases, so that the above categories are divided to a large extent by differences in amplitude as well as frequency. At the precordium they are all superimposed but may be recorded selectively by application of appropriate frequency filters.

**Failure of Cardio-Pericardiopexy to Protect Experimental Animals Against Acute Coronary Occlusion**

*Harry Gross, New York, N. Y.*

Yorkshire piglets weighing from 25 to 30 kg. were subjected to ligation of the left anterior descending coronary artery at least 2 cm. from its origin. Many animals survived. None survived if the occlusion was within 2 cm. of the origin of the artery.

Twenty one piglets were then prepared by instilling talc into the pericardium. At intervals of one to 55 weeks, the heart was exposed and the left anterior descending coronary artery was ligated within 2 cm. of its origin. None of the pigs survived and none of the hearts showed gross myocardial changes. Pericarditis was well established in every pig with an acute inflammatory reaction in the early cases and fibrosis and scarring in the later cases. There was no evidence of constrictive pericarditis, or significant increase in vasculature.

Coronary artery ligation was followed by the development of ECG currents of injury with R-T segment displacement upward or downward and numerous arrhythmias, mainly various types of tachycardia. Among these, premature ventricular beats followed by multifocal beats leading to ventricular tachycardia developed. In many instances the transition was abrupt, going from a normal sinus rhythm to a fatal ventricular tachycardia. Following the instillation of talc, T wave changes of a nondescript character were noted.

In a few animals occlusion of the coronary artery produced severe ECG changes which reverted to normal when the occlusion was released. In some, release of occlusion failed to prevent death. No increase in survival time was noted in the talc protected animals as compared to control animals when the challenge offered was the same. It is concluded that talc pericarditis does not protect the pig against acute experimental interruption of the left anterior descending coronary artery.

**Effects of Reserpine and Chlorpromazine on Central Autonomic Vasomotor Mechanisms**

*C. G. Gunn, Jr., M. Jouvet and E. E. King, Los Angeles, Calif.*

Reserpine and chlorpromazine are currently presumed to exert their main influences upon the autonomic and cardiovascular systems by affecting the central nervous system.

This study was designed to investigate the effect of these compounds in various doses upon the central efferent vasomotor systems, central afferent multisynaptic systems and the peripheral sympathetic system as a peripheral control in curarized (Flaxedil), unanesthetized cats. Thresholds to elicit minimal but definite blood pressure rises (5 to 10 mm.) were determined after monitored stimulation of the mesencephalic and bulbar reticular formations. Electric activity of the cortex and brain stem and the ECG was recorded. After assuring stability of the thresholds, either chlorpromazine (.05 to 5.0 mg. per Kg.) or reserpine (0.1 to 1.0 mg. per Kg.) was given and pressor thresholds were periodically determined for the next 2 hours. Control experiments without drugs were done for comparison.

Chlorpromazine was found to have a barbiturate-like effect, especially in higher doses, causing sleep-like cortical activity, raising the reticular formation threshold and depressing afferent evoked potentials in reticular formation, without raising the splanchnic threshold. In small doses, thresholds may be unchanged or lowered with cortical arousal, also seen in small doses of barbiturates. Reserpine, even above pharmacologic doses, had no effect on thresholds in either reticular formation or splanchnic. There was no depression in either afferent evoked sensory potentials or cortical activity. In some experiments after either drug, stimulation at pressor threshold values caused a depressor response and a rise in pressor thresholds but without a rise in the cortical arousal threshold, which remained below original pressor threshold. In these experiments anoxia or subdural hematomas seemed to be present. Arrhythmia thresholds were elevated with both drugs. These results are compatible with the hypothesis of both pressor and depressor systems in the central nervous system, which may be independently affected by drugs or altered physiologic states.

**The Basic Oscillating Mechanism of Periodic Breathing in Cardiac Failure**

*Arthur C. Guyton, Jack W. Crowell and John Moore, University, Miss.*

Many patients with severe cardiac failure develop long-sustained periodic breathing. The cause of this has been suggested to be an oscillating mech-

anism between the lungs and respiratory center. The patient first overventilates; this makes the blood in the lungs hypocapnic and overly oxygenated; then, after a delay of a few seconds, this blood arrives at the medulla; when it does arrive there, the respiratory center is depressed; this causes less ventilation and results in hypercapnic and anoxic blood in the lungs; when this blood arrives at the medulla a few seconds later, the patient overventilates again, resulting in a new cycle.

The present study was designed to test the validity of this postulated oscillating mechanism. All major vessels passing upward through the neck were ligated and the head was supplied with blood through an external circuit. The interval of delay between the passage of blood through the lungs and its appearance in the brain was varied by increasing or decreasing the volume of the external shunt. When appropriate shunt volume was established, periodic breathing of either the sustained or at least slowly damped type was attained. Furthermore, the oxygenation of the blood at the beginning of the shunt and at the end of the shunt were out of phase with each other and changing the shunt length changed the breathing periodicity, thus demonstrating the validity of the theory.

In other words, the natural oscillating mechanism for periodic breathing is present all of the time. Actual oscillation will appear when various factors, such as delay in blood flow to the head, overcome the damping mechanism of the respiratory control system.

**Physiologic Changes Seen After the Use of $I^{131}$ in Chronic Pulmonary Insufficiency**

*W. F. Hamilton, B. Shannon Gallaher, W. F. Hamilton, Jr., Irene F. La Motte, Robert G. Ellison and Lois Ellison, Augusta, Ga.*

Crippling pulmonary insufficiency was treated with $I^{131}$ by one of us (W. F. H., Jr.) in a series of 8 badly incapacitated patients. They were followed-up for a year or more beginning in Nov. 1952. The results of this treatment were so favorable that a detailed physiologic study of a second series was undertaken.

As of May 1955, 16 patients, followed-up for periods up to 14 months showed, in an equal division, excellent clinical improvement (4), good results (4) and fair results (4), while in the 4 remaining, the results were either undetermined or poor. In cases where the standard dose of 25 mc. of the radioactive iodine reduced thyroid activity, clinical improvement was in rough proportion to the change in thyroid status. In cases of "double blind controls" and in cases where the antithyroid therapy was ineffective because of previous iodine saturation or other causes, there was no significant clinical improvement.

Ventilatory status was unchanged as indicated by lack of significant improvement in maximum breathing capacity, vital capacity and timed vital capacity. Gaseous exchange was improved, because, with the change in thyroid status, less gas must be exchanged. The arterial $PO_2$ was increased, the arterial $PCO_2$ and combined $CO_2$ were decreased and the difference between effective alveolar and arterial $PO_2$ was increased. Where these changes occurred, they were accompanied by an amelioration of symptomatic distress.

**The Graphic Recognition of Predominant Mitral Stenosis or Insufficiency**

*O. M. Haring, H. Trace, C. Aravanis and A. A. Luisada, Chicago, Ill.*

A clinical and graphic study was made of 131 patients with rheumatic mitral lesions. In 25 operated cases, comparison between preoperative and postoperative tracings was possible and a follow-up study was made for a period of from 6 months to 3 years.

In all cases, ECG studies, phonocardiograms and electrokymograms of the left atrium in several projections were recorded. In 10 cases, catheterization of the right heart was performed. In 3 cases, this procedure was repeated after surgery.

Among the data which were studied before and after surgery are (1) ECG evidence of ventricular hypertrophy; (2) phonocardiographic demonstration of murmurs (systolic, diastolic), snaps (opening snap) and gallop sounds (ventricular, atrial); (3) phonocardiographic measurement of the distance between Q and the first sound and between second sound and the opening snap; (4) electrokymographic demonstration of a plateau pattern in atrial tracings with attention paid to the number of projections presenting it, height of plateau (through calibration) and time relationship (early or late plateau); (5) evidence obtained by the surgeon (H. T.) in regard to size of the chambers, thrills, size of mitral orifice and feeling of a regurgitant jet (reservations about the interpretation of these findings are presented).

Electrokymography and ECG studies were found useful for recognition of predominant mitral insufficiency or stenosis. Phonocardiography and the ECG gave data of significance in the evaluation of left atrial pressure. Catheterization was found valuable for evaluation of right ventricular and pulmonary loads.

**Relation of Potassium Ions in Extracellular Fluid to Ectopic Ventricular Arrhythmias Induced by K-strophanthoside**

*A. Sidney Harris, John E. Firestone and Richard A. Liptak, New Orleans, La.*

The administration of K salts to patients with ectopic cardiac arrhythmias has terminated the

arrhythmias in some cases. K therapy appears to have been particularly successful in abolishing ventricular ectopic beats due to toxic doses of a digitalis glycoside. Recent studies of ventricular tachycardia, produced by myocardial infarction, indicate that local increase in extracellular K concentration in the region of ischemia probably is an important factor in the causation of ectopic impulses in this condition. In cyclopropane epinephrine arrhythmias, a sharp increase in plasma potassium following epinephrine injection appears to be a factor in the production of ectopic impulses. The relation of K to ectopic impulses in digitalis glycoside toxicity, according to available evidence, seems to be different from its relation to ectopic impulses in infarction and in cyclopropane epinephrine studies.

Experiments were designed to examine critically the role of K in arrhythmias produced by K-strophanthoside in acute experiments in dogs. The dose of K-strophanthoside used to produce the arrhythmias was 0.1 to 0.14 mg. per Kg. The tachycardia has been found to be accompanied by elevation in potassium concentrations in arterial blood and in coronary sinus blood, but no consistent correlation between degree of potassium increase and onset or degree of ectopic activity is evident. Comparisons of the amounts of increase in arterial and coronary sinus samples have made it clear that the sources of excess K principally are extracardiac. Liberation from the heart undoubtedly occurs, and in some determinations the potassium increase in coronary sinus blood is significantly greater than in arterial blood. This is not consistent.

Attempts to terminate K-strophanthoside-induced ventricular tachycardia by slow intravenous infusion of KCl in an incomplete series of experiments have not been successful. Dibucaine hydrochloride has proved highly effective in terminating these arrhythmias. One action of such local anesthetics on cell membranes is reduction of permeability to K.

**Consistency of Response to Psychologic Stress in "Prehypertensives" and in Patients with Essential Hypertension**

*Robert E. Harris, Maurice Sokolow, Lewis G. Carpenter and Betty L. Kalis, San Francisco, Calif.*

A characteristic pattern of response to psychologically stressful situations has been established for college women who are "prehypertensive," i.e., who have transiently elevated blood pressure and presumably a greater probability of becoming hypertensive in later life. In psychiatric interviews and in situations utilizing psychodramas to reproduce lifelike conflicts and problems, they were typically more hostile and less well controlled than matched controls and less well equipped to cope with experimentally imposed stress. The question arose: Can the same pattern of response be found in patients with essential hypertension? A positive answer would suggest that the personality characteristics present before the onset are relevant to the development of the disease.

Fifteen women with essential hypertension, and 22 normotensives were exposed to two psychodramas like those used with the "prehypertensives." One called for assertive behavior; the other, for tact, diplomacy, and social skillfulness. A staff member played opposite the subject, sharpening the conflicts and making it difficult for the subject to carry out her assigned tasks. Staff observers did not know which subjects were hypertensive until their impressions had been recorded.

Both physiologic and psychologic response differed for the 2 groups. The hypertensives showed a greater increase in blood pressure and heart rate. Analysis of the observers' impressions were recorded on check lists and rating scales. Typescripts of the recorded interactions showed the hypertensives to have poor emotional and behavioral controls, to be less flexible and adaptive and to lack appropriate assertiveness. These characteristics are very similar to those found for the "prehypertensives." Thus, similar kinds of response to psychologic stress are found at two different age levels and two different stages of the disease. The consistency of the patterns suggests that psychologic factors may influence the development and course of hypertension.

**Unusual Clinical Features Associated with Severe Aortic Insufficiency**

*W. Proctor Harvey, Jack P. Segal, Recep Ari and Charles Hufnagel, Washington, D. C.*

Evaluation of approximately 200 cases of severe aortic insufficiency disclosed many unusual clinical features which have been unrecognized or only briefly mentioned in the literature. In over 80 per cent, the etiology was rheumatic.

The unusual features were: (1) sudden death (10 per cent), presumably due to ventricular fibrillation, usually occurred in those with frequent ventricular extrasystoles, particularly in cases with more advanced heart disease; (2) excessive "sweating" (60 per cent) was usually extensive and associated with heat intolerance; as the amount of regurgitation and failure progressed, the sweating generally increased; (3) carotid artery pain (25 per cent) was usually characterized as a throbbing pain, lasting from hours to several days, and often acute in onset; usually, there was tenderness over the carotid arteries and often enlargement of the tonsillar lymph nodes; (4) abdominal pain (43 per cent) usually associated with epigastric pounding; sharp pain in the epigastrium or right upper quadrant may be confused with gallbladder disease or peptic ulcer, even to the point of consideration of surgical

intervention; this abdominal discomfort is different from that associated with hepatic engorgement in congestive failure; (5) angina pectoris (50 per cent) was usually classical and in a few patients was predominantly nocturnal; the frequent occurrence of angina is in contradistinction to the many reports in the literature stating its rarity in the rheumatic group and (6) pallor (30 per cent) was relatively infrequent and often associated with rheumatic activity.

There was no correlation between any of these features and the presence of angina or failure, except that angina was more frequent in those with abdominal discomfort and carotid artery pain. These symptoms could not be correlated with the level of the systolic, diastolic or pulse pressures. Other unusual features following insertion of the Hufnagal plastic valve are discussed.

**Comprehensive Care of the Cardiac Patient: A Team Approach**

*William I. Heine, Sidney O. Krasnoff, Alexander Hersh, Anna D. Mitch and Louis J. Mosca, Philadelphia, Pa.*

Comprehensive care denotes a conscious effort to help the patient make an optimum adjustment. This is accomplished through a broad understanding of his disease and its relation to his emotional, social and occupational environment. It also shows a continuous interest in the patient through all phases of his illness. To effect such care for cardiac patients it became evident that routine diagnostic and therapeutic measures, offered by the physician alone, were inadequate. We have, therefore, developed a team composed of physicians and ancillary personnel. The physician as leader utilizes and integrates the contributions of the other team members. The public health nurse aids in counseling and the dietitian offers instruction and guidance in following diets and evaluates motivations, food habits, financial status and comprehension ability. The social worker helps the patient to cope with emotional, social and situational problems relating to the adjustment to his illness as it concerns his family, employment and hospitalization. The various problems are evaluated by each team member as an individual and then collectively, through planned team conferences. The essential criteria for developing and maintaining a dynamically effective team are discussed.

**Triethanolamine Trinitrate (Metamine) in the Treatment of Angina Pectoris: A Long Term Study**

*Elliot M. Heller, Toronto, Canada*

Twenty-six cases of angina pectoris were put on triethanolamine trinitrate (Metamine). Eight cases showed definite initial improvement from a minimum of 2 attacks per day to a maximum of 3 per week. All cases had a typical clinical history of angina pectoris and suffered at least one attack of acute cardiac infarction proven by history and ECG study. Thus the diagnosis of angina pectoris was definite. Before metamine therapy, the patients were observed on conservative therapy during a control period of from 6 months to 5 years. In every case, they had also received other vasodilators, notably khellin with no significant improvement, compared to the control period, except for 1 case which however did still better on metamine.

After being on metamine therapy over periods ranging from 6 months to 3 years, 6 out of 11 cases developed acute cardiac infarctions with two mortalities, while 1 case developed acute coronary insufficiency. Compared to this, the 15 cases, not on metamine therapy over a similar period, developed 2 cases of acute coronary insufficiency while 3 died of causes not directly related to cardiac ischemia. Toxic symptoms due to metamine administration were rare and slight. They occurred in only 4 cases and consisted of one or more of the following: nausea, heartburn, cough, dizziness and generalized itchiness.

**Massive Intermittent Dose Method of Dicumarol Therapy in Myocardial Infarction**

*Herman K. Hellerstein, Eugene Vayda, William B. Newberry, Jr. and Harold Feil, Cleveland, O.*

The massive dose method of dicumarol therapy, reported by Shapiro and Weiner, was used in the treatment of 47 patients with 51 episodes of acute myocardial infarction. Initial doses of dicumarol ranged from 6.7 to 15 mg. per Kg. of body weight, averaging 10.1 mg. (400 to 1000 mg.). After the initial dose in 33 instances, an intermittent dosage schedule was continued, with smaller but relatively massive doses (200 to 500 mg.), given intermittently when the prothrombin level exceeded 35 per cent. In the remaining 18 episodes, the conventional daily maintenance method was used. Prothrombin levels were determined daily and the patients were observed closely for microscopic and gross bleeding and thromboembolism.

The patients were representative of myocardial infarction, the ages ranged from 33 to 84 years, with a mean of 58 years; 40 were males, 8 females. Satisfactory therapeutic prothrombin levels (below 35 per cent) were maintained for 75 per cent of the desired time in 70 per cent of the cases. There were no serious complications due to dicumarol therapy. Minor complications occurred in 7 cases (14 per cent), with one case of spontaneous subcutaneous bleeding without hypoprothrombinemia, hypoprothrombinemia with or without microscopic hematuria or melena in 4 cases, and microscopic hematuria or melena without hypoprothrombinemia in 2 cases. Two cases were treated with vitamin $K_1$ oxide because of a rapid decline in prothrombin level, although neither reached dangerously low

levels or showed evidence of bleeding. The mortality rate was surprisingly low, 4 per cent (2 cases), although there were 36 "poor risk" patients. Neither of the 2 deaths was associated with hypoprothrombinemia or hemorrhage.

The massive intermittent dose method of dicumarol therapy is safe, effective, and avoids the danger of accumulation. As in other methods accurate daily prothrombin determinations are required.

**Physiologic Response to the Master Two-Step Test in Normotensive Patients with Coronary Disease**

*Herman K. Hellerstein, Amasa B. Ford and William K. Littman, Cleveland, O.*

The physiologic response of 38 normotensive men with coronary artery disease to the Master two-step test was compared with a control group of 116 men.

At rest, 82 per cent of the coronary group had abnormal ECG's, and 67 per cent had abnormal ballistocardiograms. In the control group, the incidence was 4 per cent and 10 per cent respectively. There was no significant difference between the coronary and strictly normal groups in age, height, weight, time required for exercise or resting oxygen consumption. Oxygen consumption above resting per minute of exercise was similar, 1.48 ± 0.19 L. per minute (5.8 times resting) in the control group and 1.32 ± 0.37 L. per minute (5.3 times resting) in the coronary group, with no significant difference with age. Work, performed at this oxygen cost, decreased significantly ($p = <0.05$) in both groups above the age of 40, but this decline in mechanical efficiency was no greater in the coronary group. The increase in oxygen consumption, due to exercise, was divided between exercise and recovery periods in a ratio of 1.17 to 1 in the normal group. The coronary group had a ratio of 0.82 (i.e., more of the oxygen cost was deferred), with a statistically significant difference in the 40 to 49 age group ($p = <0.01$). "Oxygen utilization" at rest and exercise did not differ significantly in the two groups.

Seventy-six per cent of the coronary group had abnormal recovery of pulse rate, blood pressure or ECG changes alone or in combination, in contrast to 18 per cent of the controls. Pulse recovery was the least sensitive criterion. The best discrimination between the coronary and control groups was provided by combination of abnormal blood pressure and abnormal ECG responses. This combination occurred in 34 per cent of the coronary group and in only 2 per cent of the control group.

**Plasma Factor Enhancing the Ability of Angiotonin to Cause Contraction of Rabbit Aortic Strips**

*O. M. Hellmer, Indianapolis, Ind.*

While investigating the effects of epinephrine and angiotonin on spirally-cut strips of rabbit aorta, it was observed that whereas the amplitude of contractions produced by a given dose of epinephrine remained the same or increased, the amplitude of contractions produced by angiotonin became less with each succeeding addition to the muscle bath and sometimes became negligible. The ability of angiotonin to cause contraction could be restored by the addition of human, dog, cat, or rabbit plasmas, which, by themselves, had no apparent effect. The factor in plasma which activates angiotonin is protein-like and appears to be enzymatic in nature. The product of the reaction of angiotonin with this factor does not show tachyphylaxis; since it is destroyed by incubation with red cell and kidney angiotonase as well as with trypsin, it appears to be a polypeptide. Activated and unactivated angiotonin shows the same pressor response when injected intravenously in a cat. This is probably because angiotonin activation is very rapid in the presence of an excess of plasma.

The plasma of some patients with hypertension has more of the activating factor than that of normotensive subjects. Plasma was also found to enhance the contraction produced by epinephrine and activated-angiotonin. This may be due to an effect on the muscle strip itself.

**Comparative Studies of the Effects of Various Diuretics on the Outputs of Electrolytes**

*George R. Herrmann, Reba K. Jones, R. B. Crouch and M. R. Hejtmancik, Galveston, Tex.*

The blood levels and urinary output of sodium, potassium and chlorides were determined during a 24 hour control period and for 1 to 10 days after use of each diuretic.

Fifty-seven studies, following diuresis with various mercurial preparations, showed the maximum outputs for only 2 days averaging urine outflow of Na 8.6 ×; K, 3.2 ×; and chlorides, 9.3 times that of the control day with an average body weight loss of 3 per cent. The actual average of daily amounts and total period excretions were urine, 2.6 L. and 155 L., Na, 3.2 Gm. and 186 Gm., K, 2.1 Gm. and 124 Gm. and chlorides 5 Gm. and 299 Gm.

Digitalis in 62 studies over an average of 7 days showed average urine 3.4 ×; Na, 5.0 ×; K, 3.5 ×; chlorides 6.2 times that of the control day with a body weight loss of 5.5 per cent for the period. The actual average daily amounts and total period excretions were urine, 1.4 L. and 401 L.; Na, 1.7 Gm. and 500 Gm.; K, 1.4 Gm. and 404 Gm. and chlorides 2.1 Gm. and 615 Gm.

Diamox in 25 cases over an average of 5 days showed average urine outputs 2.8 ×; Na, 5.4 ×; K, 2.8 × and chlorides, 3.9 times that of the control day with a body weight loss of 4 per cent for the period. The actual average daily amounts and total period excretions were urine, 1.6 L. and 162 L.; Na, 2.4 Gm. and 244 Gm.; K, 1.8 Gm. and chlorides, 3.7 Gm. and 371 Gm.

Aminophylline in 10 studies over an average of 2 days showed average urine outputs 2.4 ×; Na, 4.6 ×; K, 3.5 × and chlorides 3.8 times that of the control day with a body weight loss of 1 per cent for the period. The actual average daily amounts and total period excretions were urine, 1.4 L. and 21.7 L.; Na, 3.2 Gm. and 51 Gm. K, 2 Gm. and 32.2 Gm. and chlorides, 4.6 Gm. and 74.2 Gm.

Mercurial diuretics are apparently more effective but for a shorter period of time. Comparative studies of the various mercurial preparations and of the various digitalis preparations revealed no significant differences in the resulting outputs.

**The Blood Volume in Patients in Congestive Heart Failure and After Diuresis**

*George R. Herrmann, R. B. Crouch, James D. Lancaster and John E. Perry, Galveston, Tex.*

The blood volume in congestive heart failure has been restudied by various methods. In general, elevated volumes are found in chronic congestive heart failure. There are, however, occasional discrepancies and therefore, we have continued investigation of the problem of other factors that may affect the blood volume.

We have used radioiodinated human serum albumin with $I^{131}$ for determination of plasma volume and sodium chromate with radioactive $Cr^{51}$ for determination of erythrocyte mass. Calculations were made on the bases of total volumes per 1 Sq. M. of body surface areas and 1 Kg. of body weight. The hemoglobin levels and the hematocrit values were taken into consideration. The hematocrit percentages was used only in the earlier series of 35 cases in which only radioiodinated albumin was used.

We determined blood volumes with both $I^{131}$ and $Cr^{51}$ in 50 patients. In 40, the studies were made during the edematous state and after diuresis. There were 32 patients with hypertensive arteriosclerotic heart disease; 20 with anemia and 12 without; 2 with syphilitic aortitis; 2 were thyrotoxic; 6 had cor pulmonale and 10, rheumatic heart disease. In most of the severely decompensated cases, the blood volume was decreased significantly after basic diuresis.

It was noted that the patients with severe anemia had significant elevations of the blood plasma volume which decreased sharply on diuresis. The patients with polycythemia showed greatly increased red cell mass at the expense of the plasma volume and there was less decrease in volume after diuresis. The venous pressure and hemoglobin were not affected by diuresis in the 6 cor pulmonale cases. The patients with rheumatic mitral stenosis and failure showed no anemia and less elevations in plasma and total blood volume than did patients with hypertensive arteriosclerotic heart disease and failure.

**Changes in Nasal and Digital Vasomotor Tone During Cooling**

*A. B. Hertzman, D. Davis, I. D. Ferguson and A. Rampone, St. Louis, Mo.*

Three nude sitting subjects were equilibrated for 1 hour in a climate chamber and observed for an additional half hour at 32 C. Chamber temperature was lowered subsequently at a constant rate (11 C per hour) to various levels, the lowest being 16 C. Humidity was kept constant at 13 or 15 mm. Hg. Skin temperatures (10 areas) and nasal and digital photoelectric plethysmograms were recorded continuously during the entire period of observation (up to 2.5 hours). The fall in mean $T_S$ was a function of the experimental climate and the physiologic heat sink. Nasal and digital volume pulses decreased in all experiments. Assuming that blood flow varied directly with the pulse volume, nasal and digital blood flows showed a curvilinear relation to the mean $T_S$ obtaining at any moment. However, the square root of the pulse volume decreased linearly with mean $T_S$. Since other work in this laboratory has indicated that the square root function of the pulse volume is directly related to the tone of the vascular smooth muscle, we conclude that nasal and digital vasomotor tone is inversely and linearly related to the mean $T_S$. This effect could be due to a simultaneous and proportional increase in the vasomotor impulse traffic to each vascular bed. Digital blood content decreased in a regular manner but nasal blood content showed a complex relation to the mean $T_S$ and the chamber climate.

**A Comparison of the Diuretic Effect of Sodium Nitrate with Various Other Diuretic Agents in Normal Dogs**

*Edwin P. Hiatt, Chapel Hill, N. C.*

The effect of single maximal doses of several diuretic agents on the volume and composition of the urine, produced in the following 24 hours, was studied in 3 trained, unanesthetized dogs, deprived of food and water for the preceding 24 hours. The agents investigated were the Na, K and ammonium salts of nitrate, NaCl, acetazoleamide (Diamox) and meralluride (Mercuhydrin Sodium). The last agent was given by slow intravenous injection, the others by mouth. The salts (7.5 mEq. per Kg.) were given in a Na-poor vehicle, either Lonalac or washed ground meat. A similar portion of the vehicle was given in the control experiments, with the acetazoleamide and meralluride. Measurements of the urinary volume, Na, K, osmolarity, pH and nitrate were done routinely, and in some experiments, measurement of chloride and bicarbonate.

We have taken the Na excretion as the best index of the diuretic effect. In the instances where Na

salts were administered, the net Na excreted, namely in excess of the quantity administered, was taken as the diuretic action.

The 24 hour excretion of Na in the control experiments was less than 1 mEq. per Kg. The net sodium excretion after NaCl was essentially zero. The other agents caused a Na loss ranging from 1.5 to 4.5 mEq. per Kg. per 24 hours. Though sodium nitrate is slightly less effective than the ammonium and potassium salts of nitrate, it has the advantages of low toxicity by vein or mouth and little disturbance of acid-base balance. The nitrate salts were little, if any, less effective than the acetozoleamide and meralluride.

There was no net excretion of K after potassium nitrate administration. That, after the mercurial, was not greater than the controls. The other agents, in order of increasing effectiveness on K excretion, were sodium chloride, sodium nitrate, acetazolamide and ammonium nitrate with the highest rate of K excretion being about 3 mEq. per Kg. per 24 hours or about three times the control rate.

**The Image Tetrahedron in Man Determined by Reciprocal Stimulation of a Tridimensional Esophageal Electrode**

*Jacob I. Hirsch, Stanley A. Briller and Nathan Marchand, New York, N. Y.*

In an attempt to determine the electric configuration of the tetrahedral system of ECG leads, 6 leads, joining the 4 apexes of the tetrahedron were studied. Through each in turn was passed a current of constant magnitude at a frequency of 47 c.p.s. Measurements were made of 3 orthogonal components of the voltage induced by each lead current in the esophagus near the ventricles.

The equipment included a signal generator which drove a push-pull amplifier, the high impedance output of which was applied to the 6 surface leads in sequence. The esophageal pickup consisted of 3 dipoles of silver, imbedded in a small ball of thermosetting plastic. These were mutually perpendicular and of equal moment. Each dipole pair, in turn, fed into a cathode follower stage, thence through a 47 cycle band pass filter to one channel of a twin beam electrocardiograph. A monitor signal from the generator was applied to the other channel as a polarity reference. When the pickup was in place in the esophagus prior to a run, a cellophane dialysis bag filled with saline enveloped it in order to establish good contact with the esophageal walls.

The quality of each run was tested by ascertaining that satisfactory agreement existed between measured and calculated lead vector sums. The magnitude of each lead (L) was determined from components $A_L$, $B_L$ and $C_L$ since $L^2 = A_L^2 + B_L^2 + C_L^2$. Wire models were constructed from these values.

Twelve runs in 2 subjects yielded these results: (1) standard lead I was consistently the smallest; (2) lead II was consistently larger than lead III; (3) anteroposterior leads were larger than anticipated, and lead BF (back to left leg) was consistently the largest and (4) the position of the apex of the tetrahedron on the back varied greatly. The data accentuate the critical importance of dipole position in determining the form of the image space in man and indicate that the esophagus is probably too far posterior for placement of an artificial heart dipole, in attempts to estimate lead vectors.

**Tetralogy of Fallot: Review of Unusual Manifestations**

*W. E. Holladay and A. C. Witham, Augusta, Ga.*

Twenty-three cases of tetralogy of Fallot were reviewed with respect to clinical criteria by which the diagnosis is usually made. A surprisingly wide range of clinical manifestations appear to be compatible with the diagnosis. Many of these variants are not stressed or are actually contradicted in the literature and are therefore included in this report.

(1) A syndrome of hypertension, left ventricular hypertrophy, congestive failure and greatly increased transverse diameter was seen in 6 cases. At least 5 of these are dead. Infundibular stenosis is implicated in the majority. (2) The "coeur en sabot" represents the minority of cardiac silhouettes, usually occurring only in early childhood. (3) Identifiable and even prominent main pulmonary arterial trunks are sometimes seen and suggest valvular pulmonic stenosis. Approximately one fourth of the x-ray studies in this series reveal normal or increased vascular markings. (4) Intensity and age of onset of cyanosis is extremely variable and appears to be prognostically important, secondary anemias and pigmentation may obscure its presence. The acyanotic tetralogy is not a rarity (10 per cent). (5) Murmurs apparently may arise from the obstructed pulmonary artery, from the septal defect or from both locations. Auscultation and phonocardiography, however, reveal no diamond-shaped murmurs, typical of pulmonary stenosis; $P_2$ is usually loud. Absence of murmurs suggests pulmonary atresia. (6) Although difficult to understand in the presence of a septal defect, giant atrial waves were easily seen and recorded from the jugular vein in 2 instances. (7) Hypertrophy of the right ventricle may be so slight or concentric that its fluoroscopic shadow is not distorted. ECG evidence of its presence may be only suggestive. (8) The fact that minor anatomic deviations produce major clinical variations is emphasized by the high incidence in this small series.

**Relationship of Dyspnea to Acutely Induced Changes in the Pulmonary Vascular Pressures in Patients with and without Congestive Heart Failure**

*W. Hollander, W. E. Judson and R. W. Stone, Boston, Mass.*

The effects of the intravenous administration of 5 per cent sodium chloride or of hexamethonium, on cardiovascular and/or respiratory function, were studied in 2 similar groups. When 300 cc. of saline was given intravenously to patients with congestive heart failure, it caused no change in cardiac output (direct Fick), but a rise of 10 mm. Hg occurred in the pulmonary artery and in the pulmonary capillary pressures. When given to patients with chronic lung disease and cor pulmonale, it produced similar rises in the pulmonary arterial pressure, but it increased the cardiac output without changing the normal pulmonary capillary pressure. With the exception of 3 patients in congestive heart failure who had markedly elevated pulmonary capillary pressures, none of the patients experienced increased difficulty in breathing or had noticeable changes in the arterial oxygen saturation, minute, residual and total lung volumes, or intrapulmonary gas (helium) mixing. The vital capacity and maximal breathing capacity decreased only in patients with congestive failure.

Intravenous hexamethonium produced no changes in cardiac output in patients with congestive heart failure (except those with hypertension), but it did decrease both the pulmonary arterial and pulmonary capillary pressures. Associated with these latter changes, the dyspnea of congestive failure, but not that of chronic lung disease, was usually relieved and accompanied by increases in the vital capacity and maximal breathing capacity. No changes in respiratory function occurred in patients with chronic lung disease.

It is concluded that (1) acute elevation in the pulmonary arterial pressure (independent of cardiac output) does not produce or aggrevate dyspnea, but a critical rise in the pulmonary capillary or venous pressure, may do so; (2) a reduction in the pulmonary capillary and pulmonary venous pressure, rather than in the pulmonary arterial pressure, is required to relieve the dyspnea of congestive heart failure and (3) intravenous hexamethonium is of greater diagnostic aid than intravenous 5 per cent sodium chloride in differentiating cardiac from pulmonary dyspnea.

**Renal Excretion of Sodium and Water after Intravenous Infusions before and during Chronic Drug Therapy**

*W. Hollander and W. E. Judson, Boston, Mass.*

The renal responses to intravenous infusions of 5 per cent saline or 5 per cent glucose in water in 2 groups of patients with essential hypertension (compensated), before and during chronic drug treatment (rauwolfia, hydralazine or hexamethonium), were compared with those in 2 groups of normotensive subjects. Following the infusion of 300 cc. of saline given within a half hour, hypertensive patients (including those with splanchnicectomy or adrenalectomy), before drug treatment, had increased rates of Na excretion. Following drug therapy (or a restricted sodium diet), their Na excretions usually decreased towards normal levels.

Before drug treatment hypertensive patients (including those with splanchnicectomy) showed an impaired excretion of water during an infusion of 5 per cent glucose and water (12 to 15 cc. a minute) with a diuresis significantly less than that found in the normotensive group. However, the antidiuretic response, but not the changes in Na excretion after the intravenous injection of Pitressin (1 milliunit per Kg.) given at the end of the period of maximal diuresis was similar in both groups. Following antihypertensive drug treatment, water excretion increased significantly towards normal levels.

The defect in Na and water excretion in the hypertensive groups were inconsistently related to the actual level of blood pressure, renal plasma flow (PAH clearance), glomerular filtration rate (inulin clearance), to the response to Pitressin or to the control or 24 hour urinary sodium excretion. It is concluded, therefore, that the disturbance in Na and water excretion in essential hypertension, while independent of the level of arterial pressure, like the latter tends to be corrected by chronic antihypertensive drug therapy.

**The Significance of Cardiac Work Classification**

*D. V. Holman, L. H. Bronstein and S. C. Franco, New York, N. Y.*

In 1941, Goldwater opened an out-patient clinic which he called the Cardiac Work Classification Unit because it was devoted to medical problems of employable persons with heart disease. Many similar units were established in the wave of postwar interest in Rusk's *Third Phase of Medical Care.* Principles of rehabilitation are not new, but organization is and reflects the need for better medical supervision of chronic disease.

Four years ago units were organized at University and Beekman-Downtown Hospitals. These two, whose observations are the subject of report, and others more recent, developed common technics patterned after rheumatic fever studies by the affiliated clinics. We provided a needed community service, but more important, opportunity to study effects of activity upon the natural course of heart disease, precise information on which was lacking. It may be years before we have definitive answers but we have laid the foundations. We are now ready to describe our methods from a medical point of view and discuss results with 307 patients.

We conclude that this work requires clinical skill

and individual understanding and appreciation of practical problems of competitive employment. Each case was studied in 3 distinct but continuous stages: (1) diagnosis, (2) implementation and (3) supervised follow-up. Each phase had its peculiar medical problems. Our evening follow-up clinics had better than 95 per cent attendance. We believe the material collected will supply needed information about ambulatory heart disease and how to advise its management.

**Anaerobic Tissue Metabolism in Various Types of Valvular Heart Disease**

*William E. Huckabee, Boston, Mass.*

One of the fundamental changes occurring in oxygen deficient tissues is the development of an oxygen debt which is largely unrelated to the blood oxygen tension or to the rate of oxygen consumption. This oxygen debt is accompanied by deviations in cellular metabolism toward anaerobic chemical processes. The anaerobic process utilized for energy production in oxygen deficient tissues is the reduction of pyruvate to lactate. If the rate of such "primary lactate" production could be measured, it would provide an estimate of anaerobic metabolism. Unfortunately, it cannot be measured directly as total lactate, because this quantity includes also lactate which results secondarily from the mass action effect of the quantity of pyruvate present. However, by subtracting the "secondary" from the total lactate, the rate of "primary lactate" production can be calculated from the rates of accumulation of both lactate and pyruvate ions.

When this method has been applied experimentally in animals, close agreement has been found between primary lactate and oxygen debt, but none between total lactate and oxygen debt. It has therefore been used for the estimation of anaerobic cellular metabolism in various clinical states which might exhibit relative anoxia from circulatory impairment.

During mild exercise or low oxygen breathing in patients with symptomatic mitral or aortic valve disease (class II to IV), a markedly accelerated rate of primary lactate production was found to occur in substitution for the normal increases in oxygen delivery through augmented blood flow and oxygen extraction. The most marked changes were found in patients with pure mitral regurgitation who complained chiefly of severe fatigue.

In asymptomatic (class I) mitral stenosis and regurgitation, the findings were not normal. They differed from patients with dyspnea and edema, in showing no primary lactate production. Even in this early stage, however, the responses of oxygen delivery were distinctly low, relative to total tissue metabolic rate (anaerobic plus aerobic).

Pure aortic or pulmonic valvular disease and systemic or pulmonary arterial hypertension, were striking in this series in showing no abnormalities whatever in the oxygen-pyruvate-lactate relationships. In some patients of this type who showed advanced ventricular strain, changes resembling those of class I mitral disease appeared. When clinical congestive failure ensued, findings characteristic of generalized cellular hypoxia were found, as noted for class II to IV mitral disease.

**Splenorenal Arterial Anastomosis**

*Elliott S. Hurwitt, Stanley F. Altman, Bernard Seidenberg and Henry Haimovici, New York, N. Y.*

Previous reports from this laboratory have established the availability of the splenic artery as an adequate source of arterial blood to replace a compromised renal, hepatic or mesenteric artery. Splenorenal arterial anastomosis is suggested in management of hypertension, secondary to obstruction of the origin of the renal artery, in preference to nephrectomy, embolectomy or thromboendarterectomy. This procedure may preserve a kidney with obstruction in the ureter, caused by an aberrant renal artery. Extension of the scope of resectability of aneurysms involving the region of the renal arteries may be accomplished by this maneuver. Construction of a splenorenal arterial anastomosis in a case of ascending thrombosis of the abdominal aorta, with good renal function 2 months postoperatively, is shown.

**Effects of Splanchnicectomy on Cardiac Findings in Hypertension**

*George B. Hutchison and James A. Evans, Boston, Mass.*

Preoperative and postoperative findings are reviewed in a 5-year series of 149 consecutive patients submitted to splanchnicectomy for hypertension between 1950 to 1954. Cardiac involvement was the most common indication for surgical intervention in this group. There were 117 patients who had some evidence of cardiac involvement. In 46 patients, or 31 per cent of the entire group, this was the primary indication for treatment. ECG evidence of hypertrophy or strain, or both, was present in 62 per cent of patients preoperatively. Increased cardiothoracic ratio was obtained preoperatively in 33 per cent of chest roentgen examinations.

In the zero to five year follow-up the ECG patterns of strain and hypertrophy improved in 38 per cent of the surviving patients with these findings. Regression to less favorable patterns occurred in only 22 per cent. Cardiothoracic ratios decreased in 54 per cent of all surviving patients and in the subgroup with initial cardiomegaly, 81 per cent showed improvement. Myocardial infarction, angina pectoris, congestive heart failure, gallop rhythm and pulsus alternans were present in small numbers of patients. The mortality rates in patients with these findings were 25 per cent or greater. Good results, however, in some patients in these groups suggest

that these complications should not be taken as absolute prohibitions to operation. In terms of survival, there was no significant difference in the subgroups with normal and increased cardiothoracic ratios.

Three cases of rheumatic heart disease, one with aortic regurgitation and 2 with mitral stenosis, all present coincidentally with essential hypertension, are reported. All of these patients have been improved following splanchnicectomy for hypertension.

**Effect of Digoxin in Experimental Pure Mitral Stenosis with Congestive Heart Failure**

*Albert L. Hyman, John B. Stotler and William E. Jaques, New Orleans, La.*

The effect of digoxin in pure mitral stenosis with congestive heart failure was studied in 16 dogs. A supravalvular stenosis was produced in mongrel dogs using a modification of the method devised by Hamilton and co-workers.

Cardiac catheterization, femoral artery intubation, oxygen consumption and serum and urine sodium determinations were performed prior and subsequent to digoxin administration. The right atrial or ventricular end diastolic pressure, pulmonary artery pressure, pulmonary capillary pressure, systemic pressure, cardiac output, pulmonary arteriolar and systemic arteriolar resistance were determined. The animals which died were autopsied and histologic sections of the viscera were prepared.

Ventricular fibrillation occurred immediately in 1 dog and approximately one hour after completion of the studies in another. Another dog developed acute pulmonary edema and ventricular tachycardia during the studies; no measurable hemodynamic changes were observed with digitalization in 2 dogs.

In 13 dogs with measurable hemodynamic changes, the pulmonary artery pressure fell. An increase in output was noted in 1 dog, no change in another; in the remaining 12, a fall in output was observed. The pulmonary arterial resistance increased significantly (200 dynes per cm.$^{-5}$ or more) in 8 of the 14 animals. Twelve showed an increase in systemic arterial resistance. In 9 instances in which it was studied, no correlation was observed between urinary sodium excretion and measured hemodynamic changes. In six of these, a diuresis was observed. Five dogs with ascites revealed no increase in right atrial pressure. A histologic change in pulmonary arterioles was noted in only 1 dog, and this animal had the highest mean pulmonary arterial pressure. There was no evidence of right ventricular hypertrophy by ECG findings in the dogs. No significant changes in the myocardium were seen on histologic examination. In this experiment, ameliorating effects of digoxin could not be correlated with observed hemodynamic changes.

**Present Clinical Evaluation of Fifty Patients with Mitral Commissurotomy Five or More Years Ago**

*O. Henry Janton, Philadelphia, Pa.*

Fifty patients underwent commissurotomy for mitral stenosis during the years 1949 and 1950. The purpose of this communication is to present their present status with all pertinent data on both the present functional and objective findings. Forty-one of the 50 patients are living, 5 years or more after surgery. Each of these has maintained the degree of subjective improvement noted within the first postoperative year to the present time. Twenty-five (50 per cent) of the 41 living patients are considered to be in an excellent functional state living relatively normal lives. Ten (20 per cent) are considerably improved over their preoperative state and 6 (12 per cent) remain unimproved. Of the 9 deceased patients, 3 (6 per cent) were operative fatalities during the initial phase of this surgical program. The remaining 6 (12 per cent) died from 6 months to 4 years after surgery. Three of these were desperate stage IV cases at the time of surgery; 3 were in stage III but presented completely immobile, heavily calcified valves in which an ideal commissurotomy could not be accomplished.

In the opinion of the author, commissurotomy, performed properly in cases of pure or greatly predominant mitral stenosis, has been of inestimable value to the vast majority of patients so treated. The data presented supports the view that initial improvement has been maintained for a five year period and there have been no indications to suggest that this improved state will not continue for the future.

**Concerning the Geometric Shapes of Arteries and Arterioles: A Contribution to the Biophysics of Health, Disease, and Death**

*J. Vernon Jeffords and Melvin H. Knisely, Charleston, S. C.*

Consider a segment of artery between consecutive branches; is it a cylinder, or a long, slowly-tapering truncated cone?

Our laboratory is interested in the factors which determine and limit the flow of blood under 3 sharply different sets of conditions, namely, (1) during the flow of unagglutinated blood in health; (2) during disease, while the flow of pathologic agglutinated blood may still be altered back to the conditions of health and (3), during the transition from reversible pathologic flow to the impaction of great numbers of small vessels and the consequent death of the subject. The Poiseuille equation applies only to the flow of Newtonian fluids through cylindric tubes.

Measurements of the internal diameters of branchless segments of the mesenteric arteries have

been made in frogs and mice using scales mounted in microscope oculars. The data presented show that in frogs and mice all measured segments are in reality long, narrow, truncated cones. In frogs, the minimal angle of taper was 0°7′, the maximal 2°22′. The frog vessels measured were from 163$\mu$ to 500$\mu$ in diameter, and the lengths of the segments were from 800$\mu$ to 14 mm. For mice, the minimal degree of taper was 0°5′, the maximal 2°17′. The lengths of the vessel segments were from 480$\mu$ to a maximum of 1.8 mm.

The Poiseuille equation cannot apply to the flow through cone-shaped vessels. Thus, new equations, containing factors for acceleration of flow, will have to be developed. Masses of agglutinated blood cells being forced down through the lengths of cone-shaped vessels must be subjected to a progressively increased compressing force. Embolization of arteries can occur either in the middle of a cone-shaped segment or at points of branching where, as shown by other data, sharp reductions in diameter do take place.

**Vascular Responses in the Dog's Hind Leg to Epinephrine and Norepinephrine before and after Dibenzyline**

*Kenneth E. Jochim and H. Gene Ewy, Lawrence, Kan.*

In mongrel dogs under Nembutal anesthesia, epinephrine and norepinephrine (0.1 and 1.0 $\mu$g./Kg. of each) were infused intraarterially (femoral) before and after Dibenzyline (2.0 mg./Kg.). All drugs were infused for one minute at a constant rate. Peripheral resistance was calculated from continuous femoral flow, and pressure records were obtained with an electromagnetic flowmeter and a Lilly manometer respectively.

The response of any one dog to a given infusion was consistent. In all cases, the effects of the larger dose differed only in magnitude and duration from those of the smaller. The animals fell into two groups according to response to epinephrine. In group I, the resistance curve was m-shaped, with two peaks of constriction followed by a smaller dilatory phase. In group II, the curve was W-shaped, with two maxima of dilatation followed by a return to control level. After Dibenzyline, group I showed a single smaller constriction followed by a larger dilatation; group II exhibited a single larger dilatation. In all animals but one, norepinephrine caused an initial constriction, usually followed by a small dilatation. This constrictor response was generally larger in group I than in group II. Following Dibenzyline the constriction was diminished or abolished and the subsequent dilatation was increased. In all animals, Dibenzyline, by itself, produced an initial constriction folowed by a lasting dilatation.

The types of response did not correlate with initial values of any measured variables, but seemed instead to depend on individual differences in local receptor mechanisms. The family of resistance curves resulting from a given infusion in a series of dogs can be explained by assuming variations in the distribution of constrictor and dilator receptor mechanisms and in their time course of response.

**Studies of Stress in Experimental Myocardial Infarction**

*Thomas N. P. Johns and Byron J Olson, Bethesda, Md.*

A method for producing standard myocardial infarcts in small laboratory animals by coronary artery occlusion has been perfected and used extensively in various experiments during the past 2 years. Studies of infarcts have been made in mice, hamsters, rats and guinea pigs.

The method consists of open thoracotomy using positive pressure ether anesthesia and occlusion of the main left coronary artery near its origin with a silk suture. The technic is simple and quick and, in the mouse and rat, provides a large consistent infarct of the left ventricle and septum. Large numbers of animals with standard infarcts can be made available for a given study. In contrast, to "test" coronary occlusion in the dog with its unpredictable effects and high mortality, coronary occlusion in the rat provides a standard infarct with 85 per cent of animals surviving.

Recent studies have been made of the effects of stress on rats with standard myocardial infarcts at various times following coronary occlusion. The types of stress under study include (1) moderate exercise provided by running rats measured distances in a specially constructed revolving drum; (2) violent exercise using a modification of Richter's method of swimming rats to exhaustion or death under controlled conditions; (3) total body radiation and (4) artificially induced hypertension.

Stress produced by various degrees of physical exertion has been studied in a series of 400 animals at different times following coronary occlusion. Exercise during the first six hours following occlusion produces a significantly higher mortality in rats with coronary ligation than in control rats with sham ligation. Once this shock period has elapsed, however, there is no significant difference in exercise tolerance between rats with large myocardial infarcts and rats subjected to control thoracotomy. Further studies of other forms of stress emphasize the magnitude of myocardial reserve, even in the presence of large infarcts of the left ventricle.

**Observations on the Mode of Action of a Hypocholesteremic Agent**

*R. J. Jones, Oscar K. Reiss and E. L. Balter, Chicago, Ill.*

We have been interested for some time in the ability of an alcoholic extract of mammalian brain to lower the level of serum cholesterol. It appears to be effective orally in cholesterol-fed chickens and in endogenously hypercholesteremic animals or patients. In a few patients, comparisons between the effectiveness of the brain extract and of $\beta$ sitosterol have indicated that the same reduced level of serum cholesterol is achieved with each agent. Certain pertinent observations bearing on the mechanism of action of these agents have been made with radioisotope tracer technics.

In the normocholesteremic chick, where there is no significant reduction in the serum cholesterol level with administration of these agents, the specific activity of endogenously labelled $C^{14}$ cholesterol is strikingly reduced during administration of the brain extract. Similarly, in the normocholesteremic dog, an increase in turnover of serum cholesterol was noted with the feeding of this agent. In a hypercholesteremic patient, where the rate of synthesis of cholesterol (estimated from incorporation of intravenous $C^{14}$ acetate) was not greatly changed, the turnover rate for serum cholesterol was increased and the total steroid excretion in the feces was increased by this hypocholesteremic agent. This and similar studies in the dog indicate that there is at least a twofold increase in fecal steroid excretion during the period of administration of the extract. Thus, while the method by which this is achieved remains obscure, it appears that the brain fraction promotes an increased rate of excretion of cholesterol and related steroids by way of the gastrointestinal tract. Our original presumption that the brain extract promoted conversion of intestinal cholesterol to coprosterol, thereby enhancing its ultimate excretion, has not been borne out by a recently developed technic for measuring the saturated to unsaturated sterol partition in the feces.

**The Effect of Exercise on Cardiovascular and Renal Function in Hypertensive Patients before and during Chronic Drug Therapy**

*W. F. Judson and W. Hollander, Boston, Mass.*

Renal responses to exercise in the supine position in hypertensive patients (compensated), before and during chronic oral hydralazine, were compared with those in normal subjects or in patients with congestive heart failure. Similar to normal subjects (but unlike decompensated cardiac patients), compensated hypertensives, including those who had had splanchnicectomy, had only slight reductions in renal plasma flow (PAH) and glomerular filtration rate (inulin) during exercise, with a rapid recovery of these functions following exercise. These renal hemodynamic responses to exercise appeared to be related roughly to the degree of change in the simultaneously measured cardiac outputs (Fick) and pulmonary artery, and right ventricular end diastolic pressures. Unlike normal subjects (but like patients in congestive heart failure), compensated hypertensive patients had definite reductions in sodium and water during exercise which usually persisted throughout the recovery period. One adrenalectomized hypertensive patient, like a normotensive individual, did not have a significant reduction in Na and water excretion during or following exercise. During antihypertensive therapy with hydralazine in doses of 40 to 1200 mg. daily for 3 to 14 months, the renal responses to exercise were not altered in hypertensive patients, including those who had appreciable increases in their control rates of cardiac output, renal plasma flow and glomerular filtration rate.

It is concluded that (1) an abnormal decrease in Na and water excretion occurs in hypertensive patients during and following exercise but is not necessarily related to the control level of the arterial pressure and is not corrected by chronic hydralazine therapy; (2) this disturbance appears not to be mediated through the splanchnic sympathetic nervous system but may be mediated through the adrenal gland; (3) even after one year of chronic oral hydralazine therapy in hypertensive patients, the cardiac output, renal plasma flow and glomerular filtration rate may be increased over pretreatment levels.

**Slope Volume and Cardiac Output in Normal Subjects and in Valvulotomy Patients Before and After Exercise**

*Albert A. Kattus, Jr., Harold Mills, Albert B. Klug and M. Lee Pearce, Los Angeles, Calif.*

The volume determined by the slope of the downstroke of dye dilution curves was employed as an index of pulmonary blood volume in the study of 9 normal subjects, 10 mitral stenosis, 5 mitral stenosis and insufficiency and 6 aortic stenosis patients. Determinations were made at rest and during exercise in all. The patients were studied before and after valvulotomy. Cardiac output was calculated from the area of the curves. Both cardiac output and slope volume were corrected to their respective indices by dividing by the surface area of the subjects.

Cardiac Indices (CI) averaged 3.43 liters per minute in normal subjects. With exercise (supine leg bicycling) average increase in CI was 47 per cent. Resting Slope Volume Indices (SVI) in normals averaged .593 liters. This fell with exercise an average of 39 per cent in seven of the nine subjects. In two it increased. In mitral stenosis, CI averaged 2.56 liters per minute and SVI .411 liters. Exercise increased CI 36 per cent and SVI 32 per cent on the average. After valvulotomy (3 to 6 weeks)

exercise produced only a 12 per cent increase in CI but a 60 per cent increase in SVI. Patients with mitral insufficiency and stenosis behaved similarly to the mitral stenosis patients except that preoperative CI increased an average of only 16 per cent with exercise. In aortic stenosis half the patients gave results similar to the normal subjects, both before and after valvulotomy, while the other half yielded results similar to the mitral stenosis patients.

Results of these studies suggest that exercise reduces pulmonary blood volume in normal subjects as the cardiac output increases, while most patients with valvular disease increase pulmonary blood volume with exercise as the cardiac output increases. Valvulotomy does not revert this abnormality to normal.

**Use of Serum Transaminase in Detection of Myocardial Infarction in Uncertain Cases**

*Albert A. Kattus, Jr., Charles Semenson and Robert Watanabe, Los Angeles, Calif.*

In evaluating the usefulness of the Serum Glutamic Oxalacetic Transaminase (SGO-T) test, multiple determinations were carried out on 312 patients with a wide variety of diseases. Elevation of SGO-T was found in all but 1 of 73 cases of proven acute myocardial infarction.

There were 101 patients who complained of a type of pain suggestive of myocardial infarction or angina pectoris in whom the diagnosis could not be made with certainty on the basis of clinical and ECG findings. In 49 of these, the typical rise and fall of SGO-T supported the diagnosis of infarction while in 52 cases, failure of SGO-T to rise aided in excluding the presence of myocardial necrosis.

The cases in which SGO-T elevations indicated the presence of infarction consisted of four groups: (1) 28 patients in whom the ECG was abnormal but the absence of Q waves prevented the certain diagnosis of infarction; peak SGO-T levels of 50 to 600 units were found in this group and 2 patients were shown at autopsy to have subendocardial infarction; (2) 10 patients in whom ECG patterns were obscured by previous infarction; peak SGO-T elevations of 56 to 800 units indicated new infarction; (3) 4 patients, with left bundle branch block, had peak elevations of 50 to 110 units; (4) 7 patients, in whom typical ECG patterns of transmural infarction appeared 2 to 3 days after marked SGO-T elevations, had given early evidence of myocardial infarction.

Fifty-two patients complaining of substernal pressing pain had no SGO-T elevations. Of these, 26 had transient ST deviations or T wave inversions, characteristic of coronary insufficiency, 15 had ECG patterns of old myocardial infarction, 5 had left bundle branch block, 3 had normal ECGs, 2 had ventricular strain patterns and 1 had a dissecting aneurysm, proven at autopsy.

**Studies on Complete Atrio-Ventricular Dissociation with Special Reference to Stokes-Adams Syndrome**

*Herbert J. Kayden and Maria Stack, New York, N. Y.*

The cardiovascular effects of intravenous atropine and intravenous and sublingual isopropylnorepinephrine in 10 patients with complete heart block have been compared. Atrial acceleration was obtained with both drugs, the amount of increase appeared to be related to the amount of the drug. Ventricular acceleration rarely resulted from atropine but isopropylnorepinephrine was an effective stimulator of the idioventricular pacemaker, though the dose required to obtain acceleration varied widely from individual to individual. In any given patient, the degree of ventricular acceleration was proportional to the dose used but the duration of effect did not show the same relationship. One patient had a marked elevation in systolic blood pressure, but the diastolic level was unchanged. The ECG findings showed marked variations in the configurations of the idioventricular complexes under the influence of the drug.

Two patients with complete atrioventricular dissociation had recurrent Stokes-Adams syncope due to ventricular tachycardia and ventricular fibrillation. The ECG between attacks showed ectopic ventricular focuses, in addition to the idioventricular pacemaker; these focuses were thought to be the same as in the sustained tachycardia. Isopropylnorepinephrine was administered by continuous intravenous infusion to accelerate the idioventricular pacemaker, thereby preventing aberrant ventricular beats and ventricular tachycardias which lead to the recurrent attacks of syncope. One patient was successfully treated for 60 hours and the other for 1 week. The latter patient was then placed on sublingual therapy and had no further episodes of Stokes-Adams syndrome, although he remained in complete atrioventricular dissociation.

These observations suggest that the maintenance of a more rapid idioventricular pacemaker is a more effective therapeutic approach in the treatment of recurrent ventricular tachycardia and ventricular fibrillation than attempting to depress ectopic ventricular foci. Previous studies have stressed the dangers and ineffectiveness of quinidine and procaine amide for these situations.

**Clinical Applications of Blood Vessel Replacement**

*Edward B. C. Keefer, Abel A. Lazzarini and Frank Glenn, New York, N. Y.*

The present day enthusiasm for surgery of major blood vessels is a gratifying tribute to the increasing successes with arterial transplants. Blood vessel replacement has now become an accepted, established procedure in cardiovascular surgery and in many major operations, when bridging of a vascular defect is required. Malignancy, involving important arteries, no longer prohibits resection in cancer surgery. This paper discusses the general principles of vascular replacement, clinical use of homologous arterial grafts and the functions of the vessel bank. Methods of obtaining, sterilizing and preserving arterial grafts are discussed in detail. The use of plastic prostheses is evaluated. A critical comparison of homologous arterial grafts, venous grafts and prosthetic substitutes of several materials are presented.

Clinical studies were recorded on the first 150 human homologous arterial transplants supplied by the New York Blood Vessel Bank since July 1949. A representative series of 12 cases are given, illustrating the disease process, type and location of the lesion and method of graft implantation. Homologous arterial graft transplants in humans with a maximum postoperative follow-up of five years are discussed. Profitable avenues for further research in this new field are also suggested.

**Cardiac Anaphylaxis**

*Aaron Kellner, Mario Penna and Abraham I. Schweid, New York, N. Y.*

The isolated and perfused hearts of guinea pigs previously sensitized to crystalline streptococcal proteinase, bovine gamma globulin, or crystalline ovalbumin were found to react in a striking fashion when minute quantities (0.02 to 2.0 μg.) of the sensitizing antigen were added to the perfusing fluid. The rate of contraction increased almost immediately to twice the initial rate or more; there was usually a marked increase in amplitude of contraction and cardiac arrhythmias, such as premature contractions, A-V dissociation and complete heart block often supervened. Reactions generally lasted 15 to 30 minutes, and in most cases the heart was then refractory even to a 10 or 100-fold increase in the quantity of antigen. The reaction was specific and could be elicited only by the same antigen that had been used to sensitize the animal during life. Hearts from normal, non-sensitized guinea pigs failed to react even when several 1000 times as much antigen was employed.

Two further observations were made to determine whether the anaphylactic reaction observed represented a response of cardiac muscle itself or whether it was secondary to constriction of the smooth muscle of the coronary arteries. Coronary blood flow was measured in all experiments, and no consistent changes that could be correlated with the reaction were noted. In addition, the isolated auricles from sensitized guinea pigs were set up in a water bath and the rate and amplitude of contraction measured. Reactions comparable to those seen with the isolated heart were observed when such preparations were exposed to the sensitizing antigen in concentrations as low as 0.001 μg. per cc.

These experiments indicate clearly that cardiac muscle per se participates in tissue sensitization and is capable of responding directly in anaphylaxis. This phenomenon may explain some instances of sudden death during anaphylactic reactions in human beings, and it may also play a role in the cardiac changes observed in association with hypersensitivity states.

**Suggested Nomenclature for Semilunar Valves and Commissures**

*Andrew Kerr, Jr. and Charles M. Goss, New Orleans, La.*

Identification of the semilunar valves is confusing. Many case reports and autopsy protocols fail to identify the leaflets clearly. The standard anatomic systems depend upon orienting the heart in different anatomic positions. Slight rotation from these positions will alter the designation of the leaflets. This difficulty can be overcome by using a nomenclature based on embryologic considerations. At about the age of 6 weeks, before splitting of the truncus arteriosus, two leaflet anlagen are found in each great vessel adjacent to one another. When the vessels divide, the commissure between the valve leaflets in each of these vessels remains opposite the commissure of the other great vessel.

Inspection of 115 hearts revealed that a commissure of the aorta lies opposite a commissure of the pulmonary artery in 114 specimens. It is proposed that this commissure be known as the adjacent commissure. The valve leaflets would be designated as right or left adjacent to either vessel, when looking toward the adjacent commissure. The valve leaflet, opposite the commissure, can be designated as the opposite cusp. The sinuses of Valsalva could take their names from the leaflets. The other commissures would be right or left in each vessel as one looks toward the adjacent commissure.

The nomenclature is particularly useful for rapid identification of the leaflets in necropsy specimens. The designations remain the same, regardless of the position in which the heart is held.

**Factors Related to the Prevalence of Coronary Heart Disease In Nine Population Samples in South Africa**

*Ancel Keys, B. Bronte Stewart, John F. Brock, Aileen Moodie, Margaret Haney Keys and A. Antonis, Minneapolis, Minn. and Cape Town, S. A.*

Examination of the experience of physicians and of hospital admissions and autopsies confirms long-

standing opinion that severe atherosclerosis and coronary heart disease in South Africa is very rare among (1) the Bantu, relatively uncommon among (2) Cape Town Negroes but (3) very frequent among the local white population, whose mode of life resembles that of Americans. There are no such extreme differences between these 3 population groups in the prevalence of hypertensive or other non-coronary heart disease. It is locally believed that the frequency of coronary heart disease in South Africa is related to relative income within "racial" groups, as well as in intergroup comparisons. Dietary surveys indicated marked differences in the percentage of total calories derived from fats; the averages in Cape Town are 16 per cent for the Bantu, 25 per cent for Negroes and 35 per cent for the low-income whites, while the diets of the high-income white population has an even higher fat content.

A detailed study was made of 588 clincially healthy men, aged 20 to 60, in Cape Town, divided approximately equally among the 3 groups and, within each group, among 3 income classes. Dietary fat intake, relative body weight, bodily fatness (subcutaneous), blood pressure, ECG characteristics, serum total cholesterol and cholesterol in $\beta$-lipoprotein (separated by paper electrophoresis) and cigarette consumption were estimated for each man.

Smoking was common in all groups and there was no important difference in the distribution of blood pressure. Relative overweight and obesity were more common among Europeans than among Negroes and Bantus, but very thin and very fat men were frequent in all 3 groups. Dietary total fat intake differed sharply between the groups and was related to income, this relationship being very marked among Bantu and least prominent among whites, with Negroes being intermediate. The differences in fat intake were determined primarily by differences in animal fat in the diet.

Serum cholesterol concentration differed greatly in men of the same age in the 3 groups and, according to diet, fat varied within these groups. The cholesterol in the $\beta$-lipoprotein fraction was even more clearly related to the diet fat habitus and the percentage of the total cholesterol found in the $\beta$-lipoprotein fraction tended to rise with increasing fat in the diet. Among the Bantus and to a smaller but still a marked extent among Negroes, serum total and $\beta$-cholesterol tended to rise with increasing body fatness but this was not true among the white population. The data indicate that among the items under analysis, the proportion of animal fat in the diet is the most important determinant in the observed differences in the blood and in the incidence of coronary disease. The possible role of physical activity is also discussed.

**Cholecystectomy in Patients with Coronary Heart Disease**

*John R. Keys, Thomas J. Dry, Waltman Walters and Robert Gage, Rochester, Minn.*

A study was undertaken to determine the operative risk of cholecystectomy for patients with coronary heart disease and whether removal of a diseased gallbladder influenced the subsequent course of the patient with coronary heart disease. There were 100 patients in the series. The actual surgical procedure was well tolerated and there were no deaths or other serious complications on the operating table. Three patients died in the hospital; one from acute pancreatitis on the fourth postoperative day, another from pancreatic necrosis on the twenty-first postoperative day after surviving a pulmonary embolus on the seventh postoperative day. The third patient died on the seventeenth postoperative day. This patient had cardiac failure and suffered from a cerebrovascular accident earlier in the postoperative course, neither seemed directly responsible for his death. Necropsy was not permitted in this case. The postoperative morbidity rate was not unusual for intra-abdominal procedures in patients of the age of these patients. One patient had an acute myocardial infarction after operation from which he recovered and 2 other patients had clinical and ECG evidence of acute coronary insufficiency during their hospital stay.

The survival rate of this group of patients for 7 years after operation was 70.6 per cent as compared with 83.9 per cent in the normal population of similar sex and age. This study establishes the relatively low risk of cholecystectomy in patients with symptomatic coronary heart disease and emphasizes the dangers inherent in the complications of chronic biliary disease itself. Such complications must be considered even more serious in patients with coronary heart disease. It is doubtful whether removal of a diseased gallbladder influences the course of coronary artery disease directly but it is likely that life may be prolonged by preventing the serious complications of biliary disease by performance of cholecystectomy, preferably during the quiescent phases of gallbladder disease.

**Survival Rates After Acute Myocardial Infarction with Long Term Anticoagulant Therapy**

*John W. Keyes, Ellet H. Drake and F. Janney Smith, Detroit, Mich.*

This paper reports on a controlled series of patients suffering from one or more acute myocardial infarction, who have been placed on long term anticoagulant therapy and observed for periods varying from 6 months to 5 years. The predicted survival time method has been used to evaluate the results statistically.

The first group included patients with single infarcts and subsequent severe angina or insufficiency. Among the treated cases, the death rate of patients was 3 times greater without anticoagulants than with long term therapy. In the recurrent infarct group, patients survived 2 or more myocardial infarctions, but did not necessarily suffer from recurrent angina and coronary insufficiency. Here the death rate in the control group was 5 times higher than that in the treated cases. A total of 12 deaths occurred in the 121 treated cases against 112 deaths in the 234 cases in the control group. In all, 28 treated patients terminated their therapy for various reasons including operations, a feeling by their physician that need for such protection no longer existed or for some personal reason. A total of 14 new infarcts occurred in the 28 who ceased therapy and 6 of these were fatal. Minor hemorrhagic manifestations occurred frequently and were serious in 16 cases. In 3 patients, hemorrhage apparently started a chain of events which led to the patient's death. However, in none of these did the patient actually die of exsanguination.

A reliable laboratory, able to carry out accurate prothrombin determinations, preferably done by the same individual, is necessary for the success of this treatment. In adition it is necessary to have the complete cooperation of the patient and his family, since this program imposes a rather rigid discipline on his way of living.

**Neurogenic Factors in the Chronic Phase of Experimental Renal Hypertension in the Dog**

*P. Kezdi, Chicago, Ill.*

In the dog, experimental narrowing of both renal arteries leads to chronic hypertension, while narrowing of one renal artery results usually only in transitory blood pressure elevation. No elevated renin levels can be detected in the later or chronic stage of experimental renal hypertension. Some other mechanism sustains hypertension at this stage. To investigate the role of the sinoaortic regulatory system in the chronic stage of experimental renal hypertension in dogs, one renal artery was constricted by a Goldblatt clamp, following temporary interruption of the carotid sinus nerves at their connection with the glossopharyngeal nerve. The cut ends were brought together to secure later return of function. The sympathetic innervation of the carotid sinus was permanently disrupted to interfere with the normal tone of the arterial wall.

In 11 out of 13 animals so prepared, significant hypertension resulted following unilateral narrowing of one renal artery. In 5 control animals, without carotid sinus and sympathetic nerve interruption, hypertension did not occur. The period of observation varied from 6 to 18 months. The carotid sinus function was tested by clamping the common carotid arteries before and after development of hypertension and showed that the return of function occurred between 3 and 6 months after disruption. The Etamon test was negative in the early stage of hypertension in all the animals. This response corresponded well with the return of the carotid sinus function. Hypertension persisted in 3 animals in which the constricted kidney was removed a year or more after development of hypertension.

It is concluded that the usual transitory nature of hypertension, following unilateral renal artery constriction in the dog, is dependent on a normally functioning buffer nerve mechanism. If this is suspended in the early phase, hypertension persists and leads to irreversible changes in the stretch-sensitive arterial walls. Thus, the maintenance of hypertension is shifted, at least in part, from humoral to neurogenic factors in the chronic stage.

**Comparison of Clinical and Renal Hemodynamic Effects of the Alkaloid Rescinnamine and the Alseroxylon Fraction of Rauwolfia Serpentina in Patients with Arterial Hypertension**

*Walter M. Kirkendall, Robert I. Lubin, George S. Anderson and James W. Culbertson, Iowa City, Ia.*

Observations show that the purified alkaloid reserpine, the most commonly used hypotensive fraction of *Rauwolfia serpentina,* may be responsible for accentuation of depressed states, development of Parkinsonian-like syndromes and, at times, oversedation, difficult to detect clinically. Rescinnamine (trimethoxycinnamic ester of methylreserpate) is another purified alkaloid of *Rauwolfia serpentina* which is also in the alseroxylon fraction. Animal studies suggested that the drug has hypotensive, sedative and bradycrotic effect similar to those of reserpine. To appraise its effect in hypertensive patients, rescinnamine was given to 10 hospitalized patients for 3 to 8 weeks after an adequate control period. These results were compared with results in similar groups of hypertensives, given placebos and alseroxylon action.

Our data demonstrate that rescinnamine has a moderate (10 per cent systolic and diastolic) hypotensive effect, similar in degree to that of the alseroxylon fraction (12 and 13 per cent); both were greater than the blood pressure fall in the placebo group (5 and 5.7 per cent). However, no significant bradycardia was noted in the rescinnamine patients, there being a 4.8 per cent fall in pulse rate compared to a 4.6 per cent fall in placebo and a 24 per cent fall in the alseroxylon groups. These data are of interest in that they demonstrate that characteristic effects of *Rauwolfia serpentina* can be separated in its purified fractions. Although

fewer sedative effects were seen in the rescinnamine patients compared with the reserpine treated group, our data on this point are meager and inconclusive.

Renal function studies were done on the placebo, alseroxylon and rescinnamine groups before and after therapy because no such studies have been done after chronic administration of the alseroxylon fraction or rescinnamine. Our data revealed no significant change in renal blood flow, glomerular filtration rate or filtration fraction after 2 to 8 weeks of treatment.

**Simultaneous Esophageal and Standard Electrocardiographic Leads for the Study of Cardiac Arrhythmias**

*Albert D. Kistin and James C. Bruce, Washington, D. C.*

The value of esophageal ECG leads for the study of cardiac arrhythmias is well established and depends on the demonstration of large distinctive P waves which may be absent in other leads, but the authors found 2 difficulties. It is sometimes impossible to distinguish the QRS complex from the P wave or to separate them when they are superimposed, because their component rapid deflections may be similar and their relative sizes may vary widely, P being equal to, larger or smaller than QRS. Also the differences in configurations of QRS and even P may be more apparent in other leads. The use of simultaneous standard leads obviates these difficulties, and the authors propose this as a useful method for practical diagnosis and theoretic study.

Only a few tracings of simultaneous esophageal and standard leads have been published, mostly to show the limitations of the standard leads. These limitations are demonstrated in some of the authors' cases, but the authors emphasize in other cases that the two types of leads may be complementary.

Esophageal and standard ECG leads are complementary in: (1) atrial flutter with multifocal ventricular systoles or varying aberration of ventricular conduction; (2) premature atrial systoles with aberrant conduction; (3) premature atrial systole followed by P waves different from the sinus and premature atrial P; (4) A-V dissociation, 2 types of P, recognizable only in the esophageal lead, and 2 types of QRS, recognizable in lead 3; (5) atrial tachycardia with alternating bidirectional P and 2 to 1, sometimes 4 to 1, A-V block; (6) atrial parasystole, different atrial focuses, recognizable in leads 2 and $V_1$, not in the esophageal lead; (7) retrograde conduction to the atria from premature ventricular systoles and in ventricular tachycardia, and (8) reciprocal beats after premature ventricular systoles and after delayed atrioventricular conduction.

**Bronchospirometric Determinations of Pulmonary Function in Dogs after Unilateral Ligation of the Pulmonary Vein and Artery**

*William F. Kistner, J. Gerard Mudd and C. Rollins Hanlon, St. Louis, Mo.*

Recent evidence has indicated that unilateral complete pulmonary vein ligation in the dog is not only compatible with a low mortality but also allows some return of function in the operated lung. Hanlon showed that antibiotic protection permitted the survival of a high percentage of the animals. A pathologic study by Wyatt indicated that there was little morphologic damage to the lung parenchyma 3 months after operation.

Hurwitz's studies demonstrated a small but definite residual respiratory function in the canine lung with complete pulmonary venous occlusion. Bloomer studied respiratory function in dogs with complete pulmonary artery ligation of one lung and found a significant residual function which gradually increased over a period of months.

Bronchospirometric and blood oxygen saturation data have been obtained on 21 dogs; 10 had complete pulmonary vein ligation and 11 complete pulmonary artery ligation of one lung. Periodic studies have been made 10 to 18 months postoperatively.

Within 3 months after surgery, the ventilatory function of the operated lung after either procedure is approximately 66 per cent of its preoperative level. The respiratory function (oxygen consumption) suffers somewhat more from arterial ligation than from venous ligation. The oxygen uptake in the lung with complete venous occlusion is about 50 per cent of the control level, while in the lung with complete artery ligation the oxygen consumption falls to 25 per cent of the preoperative state. These percentages remain fairly constant during the period of study.

Oxygen saturations determined on blood drawn from the azygous vein in the postoperative animal have proved to be definitely higher than in the control animal and confirmed Hurwitz's suggestion that this is a main channel of return of blood from the ligated lung to the right heart. These studies support the view that significant ventilatory and respiratory function remain in the canine lung after complete pulmonary artery or pulmonary vein ligation.

**The Action of Iodoacetate on the Electric and Mechanical Activities of the Isolated Perfused Frog Heart**

*Morris Kleinfeld, Edward Stein and John Magin, New York, N. Y.*

Microelectrodes were inserted into the interior of single ventricular fibers of the isolated perfused frog heart. The effects, of $5 \times 10^{-5}$ M iodoacetate

on the intracellular potential, on the indirect ECG, and on the direct cardiac output, were recorded. Prominent changes in both the electric and mechanical properties were observed. The most consistent, early change was a shortening of the action potential duration ($AP_d$) which was progressive. Coincident with this a shortened S-T interval and abnormal T wave were observed in the indirect ECG. Of lesser frequency was a prolongation of the P-R interval. A decreased height in the membrane action potential (MAP) with impaired depolarization occurred relatively late. The change in mechanical activity was represented by a progressive decrease in cardiac output, stroke volume and heart rate. Atrial activity persisted for some time after ventricular arrest. The alterations in mechanical activity were usually paralleled by changes in the repolarization phase of the action potential duration (shortened $AP_d$) of the ventricular fiber. The addition of substrates, such as pyruvate (0.0055 M) and acetate (0.0055 M) to the iodoacetate-treated heart, produced only a partial recovery and delay of ultimate deterioration of cardiac activity. The result was similar when adenosine triphosphate (ATP) ($1.0 \times 10^{-4}$ M) was added.

The results confirm the previous observations of the effect of iodoacetate on the mechanical activity of the heart, but are at variance with the findings and conclusions with regard to the electric activity. The recording of several parameters of the electric potentials, in contrast to only the height of the surface action potential as measured by Gardner and his co-workers, revealed an early effect on the electric properties which mirrored the changes in cardiac output.

The inability of added pyruvate, acetate and ATP to restore the cardiac activity suggests that, under the conditions of these experiments iodoacetate has other actions in addition to that of a specific inhibitor of triose-phosphate dehydrogenase. In line with Hodgkin's theory of membrane permeability, it is postulated that the enhanced repolarization phase is associated with an increased permeability of the cellular membrane to $K^+$. Love and his co-workers observed an increased outflow of $K^+$ and a net gain of $Na^+$ in human erythrocytes, following exposure to iodoacetate. This observation lends support to this postulate.

**Post Extra-Systolic T Wave Changes**

*Robert M. Kohn and John F. Filippone, Albany, N. Y.*

Changes in the T waves of post extra-systolic complexes have been noted before, but their significance remains a matter for speculation. The authors were interested in the statistical value of such changes in detecting organic heart disease. Accordingly, 5,000 tracings from the files of the Heart Station at the Albany Hospital were reviewed and 693 tracings with ectopic complexes were analyzed. All tracings included the standard 12 leads, including the augmented limb leads and unipolar precordial leads. Of the 693 tracings, 338 were satisfactory for analysis.

The cases with cardiac disease were divided into 2 groups on the basis of normal or abnormal ECGs. Those with normal tracings and heart disease had unequivocal evidence of heart disease by history or physical examination. In the group with abnormal tracings, the presence of post extra-systolic changes were analyzed and no significant correlation was noted. In the group in which the ECG was normal, except for the presence of post extra-systolic changes, the results were statistically significant. There was a definite correlation between the lowering of T waves and the presence of heart disease.

**Transcapillary Migration of Radioactive Sodium$^{24}$ Through the Pulmonary and Forearm Capillary Beds of Man**

*Renato D. Kovach, Lawrence S. Lilienfield, Lee Hershenson and Edward D. Freis, Washington, D. C.*

A study was made of the behavior of $Na^{24}$ in its passage through the pulmonary vascular bed, following antecubital vein injection of a mixture of non-diffusible $I^{131}$-albumin and diffusible $Na^{24}$. Blood was continuously sampled at 4-second intervals from the femoral artery. The samples were centrifuged, supernatant plasma was pipetted into planchets and the $\beta$ emissions of $I^{131}$ and $Na^{24}$ were counted with an end-window Geiger-Muller tube. Separate counts were obtained by applying a differential decay technic.

By comparing the observed $Na^{24}$ to $I^{131}$ ratio in each sample to the known $Na^{24}$ to $I^{131}$ ratio of the injectate, a small or negligible loss of $Na^{24}$ was found. By plotting the time-concentration curves of the sodium and iodine counts on semilogarithmic paper, extrapolated for correction of recirculation, calculation of the total percentage loss of sodium in one circulation was 5.5 per cent of the injected (S.D. $\pm$ 8.5). This small loss may represent red cell penetration of $Na^{24}$ during the period between the sampling and centrifuging of blood, rather than transcapillary migration from the pulmonary capillaries. This study provides further evidence that the pulmonary capillaries may be relatively impermeabile to electrolytes and/or that the pulmonary interstitial tissue space, available to sodium, is extremely small.

These findings were in sharp contrast to the behavior of sodium in the forearm capillary bed. Here we found a large immediate transcapillary loss (70 per cent or higher) with subsequent return of part of the electrolyte to the intravascular com-

partment, indicating a large extravascular distribution of $Na^{24}$ in the forearm.

**The C-reactive Protein Determination as a Diagnostic Aid in Coronary Disease**

*Irving G. Kroop, Peter Wedeen and N. H. Shackman, New York, N. Y.*

C-reactive protein (CRP) is an abnormal serum globulin formed by the body in response to such varied stimuli as tissue necrosis, infection and neoplasia. Serial determinations in 100 patients indicate that a positive serum C-reactive protein determination can be a sensitive indicator of myocardial necrosis and inflammation in coronary disease, provided other unrelated infectious and noninfectious stimuli are absent.

C-reactive protein was detected in every case of transmural infarction with Q waves in the ECG. A delayed positive test in some of these patients suggested that a certain degree of myocardial necrosis and inflammation was necessary before C-reactive protein appeared in the serum. It was absent initially during the premonitory phase of acute coronary occlusion, before the appearance of Q waves and clinical evidence of necrosis. These observations indicate that serial C-reactive protein determinations are essential before a negative test is considered significant.

Serial tests, late in the course of myocardial infarction, help to evaluate the decrease of myocardial necrosis and inflammation. A persistently or recurrently positive test during convalescence is usually indicative of progressive infarction, phlebothrombosis or of some other complication.

The test has been negative in all patients with coronary insufficiency and no clinical or laboratory criteria for necrosis. The test has been most helpful in acute and chronic coronary disease with RS-T and T waves changes, where the diagnosis of myocardial necrosis is difficult because of a previously elevated sedimentation rate, a normal or equivocal fibrinogen level and leucocyte blood count and an afebrile course. Previous transmural infarction, complete heart block, chronic gallbladder disease, hiatus hernia and peptic ulcer may add to this difficulty in diagnosis. In these patients, a positive C-reactive protein test indicates a significant degree of myocardial necrosis.

**Relief of Lipemia-Induced Angina Pectoris by Intravenous Heparin**

*Peter T. Kuo and Claude R. Joyner, Philadelphia Pa.*

We recently reported that in a small number of patients with severe coronary artery disease and angina pectoris, anginal pains could be regularly induced 3 to 5 hours after the ingestion of a fatty meal, when their postprandial lipemia was near its peak value.

The present report deals with the study of the effect of intravenous heparin on these lipemia-induced anginal pains. Intravenous injection of 5 to 25 mg. of heparin without the knowledge of the patient, relieved 14 of the 15 attacks of anginal pain in 5 to 7 minutes in 7 patients, irrespective of the duration of their pain. This was accompanied by reversion of the ECG, ballistocardiogram and pneumogram to their respective control levels. Similar results were obtained on 5 occasions in two patients with nitroglycerin. Intravenous saline injections produced no effect in 4 trials. Administration of 25 mg. of protamine intravenously to 1 patient produced no immediate effect. He developed severe substernal distress 30 minutes later, which was promptly controlled by heparin. In one patient two anginal attacks were initially relieved by nitroglycerin but the symptoms recurred 35 minutes later. They were subsequently controlled by intravenous heparin.

Heparin administration at the height of postprandial lipemia caused a reduction of the neutral fat and other lipoprotein zones on paper electrophoresis and a decrease in serum neutral fat content. Serum cholesterol and phospholipid levels, however, were not significantly altered either by fat ingestion or by heparin administration. This study suggests that the effect of heparin in lipemia-induced angina lies mostly in its ability to reduce and disperse the postprandial rise of plasma chylomicrons.

**Serum Glutamic Oxalacetic Transaminase as an Index of Acute Heart Muscle Cell Damage**

*John S. LaDue, Irwin Nydick and Felix Wróblewski, New York, N. Y.*

Serum glutamic oxalacetic transaminase (SGO-T) is a specific tissue enzyme whose activity is greatest in heart muscle. Its concentration in heart muscle is ten thousand times as great as in the serum, and this enzyme constitutes approximately two per cent of the dry weight of the heart. Injury to the heart is followed by a decrease in the SGO-T activity in the injured tissue and by an increase in the activity of the serum. A relatively simple, rapid reproducible spectrophotometric method has been developed and the SGO-T followed after myocardial injury.

Experimentally there is a uniform increase in SGO-T activity following ligature of coronary arteries of the dog or after injection of plastic microspheres into the coronary sinus and the increase is proportional to the amount of infarcted muscle. Two to ten-fold rises in SGO-T activity have been found in 98 of 100 patients within the first 24 hours following unequivocal acute transmural myocardial infarction. The level of SGO-T

was roughly proportional to the size of the infarct. Increased activity was observed for 3 to 7 days and tended to remain elevated in direct proportion to the peak levels.

Several patients whose ECG picture was equivocal because of the presence of bundle branch block or Wolff-Parkinson-White syndrome clearly had acute infarction as indicated by an increase in SGO-T activity.

Myocardial ischemia produced in dogs and represented by significant S-T segment displacement and T wave inversion in the ECG was not associated with an increase in SGO-T activity. In a few animals where the levels were significantly elevated following reversible coronary narrowing gross or microscopic evidence of muscle cell damage was found. Fifty of 60 patients with recurrent coronary insufficiency or status anginosus associated with negative T wave changes and/or S-T segment deviation failed to develop any increase in SGO-T activity. Ten had minor elevations and were thought to have sustained some myocardial damage.

The injection of papain into rabbits produced patchy changes in the myocardium not unlike those encountered in rheumatic carditis. Such changes were always associated with an increase in the SGO-T activity proportional to the degree of damage. Seventeen of 26 patients with active rheumatic carditis developed increased SGO-T activity.

SGO-T activity does not increase in infectious, degenerative, neoplastic, allergic, reactive or congenital disease states unless associated with acute damage to heart or skeletal muscle, or to the liver or kidney. SGO-T activity does not parallel the changes in erythrocyte sedimentation rate, white blood count, C-reactive protein or fibrinogen levels.

**Variations in Serum Glutamic Oxalacetic Transaminase Activity Following Experimental and Clinical Coronary Insufficiency**

*John S. LaDue, Irwin Nydick and Felix Wróblewski, New York, N. Y.*

The activity of serum glutamic oxalacetic transaminase (SGO-T) has been shown to be increased following experimental or clinical myocardial infarction. Furthermore, the peak level of SGO-T was roughly proportional to the extent of myocardial necrosis. Clinically, elevations 2 to 10 times the normal range have been observed in all but 8 of 300 patients, following acute transmural myocardial infarction. These observations prompted the studies of SGO-T by experimental and clinical coronary insufficiency.

Experimental reversible coronary insufficiency was produced in mongrel dogs by placing a ligature loosely about a major coronary artery and burying the ends subcutaneously so that they could be tightened at a later date. After the dog had recovered and the SGO-T has fallen to normal limits, (5 to 10 days), the ends of the ligatures were lifted producing partial occlusion of the coronary vessel. This maneuver resulted in marked S-T segment and T wave abnormalities which were reversible in that the ECG returned to the pre-occlusion level immediately upon release of the ligature. SGO-T levels were obtained daily for 5 to 10 days and then the animals were sacrificed.

Transient elevations of SGO-T were noted in 2 of 11 such experiments. The SGO-T remained entirely within normal limits in the remaining nine dogs. No evidence of heart cell injury was found at autopsy of any of the animals. In 3 additional dogs, the SGO-T rose significantly, despite the fact that the artery was not ligated and all showed myocardial infarction at autopsy. The concentration of glutamic oxalacetic transaminase in the areas of muscle made ischemic by the above technic was the same as that from control areas of the same heart. The concentration of SGO-T in infarcted myocardium was significantly lower.

Thirteen of 39 patients with recurrent coronary insufficiency or status anginosus showed minimal elevations of the SGO-T 24 to 48 hours later. In the remainder, despite marked T and S-T wave changes, the transaminsae activity remained within normal limits throughout the period of observation.

**Surgical Correction of Atrial Septal Defects**

*Conrad R. Lam, Detroit, Mich.*

The feasibility of the closure of defects of the interauricular septum is now well known. However, some of the first methods employed have been found to have shortcomings and as a result, there has been interest in open methods carried out during hypothermia. With the idea of avoiding hypothermia for defects of the more common *septum secundum* type, a technic has been devised which makes use of a two-pointed needle which permits application of a row of interrupted sutures which accurately closes defects of any size. Fourteen of these defects were closed without a death.

Four *septum primum* defects were encountered and these could not be closed. Two of the patients died following exploration. Following this experience, arrangements were made to refrigerate the *septum primum* cases as soon as the type was discovered and to carry out a plastic procedure on the open heart.

This plan was used when exploration of the auricle in a 30 year-old woman with some cyanosis who revealed two interatrial defects. One opened into a chamber which received the four pulmonary veins and the other opened into a second left atrium with the mitral valve at the bottom. With complete cessation of circulation for 15 minutes under hypothermia, a plastic procedure was carried out on the interior of the auricles, converting the two left

auricular chambers into one and finally separating the left from the right auricle. The brain and heart tolerated this procedure and the patient is well.

**Alternation of A-V Conduction Time**

*Richard Langendorf, Chicago, Ill.*

Alternation of A-V conduction time has been described in the experimental animal in the presence of A-V block or with rapid stimulation of the auricles. The purpose of this paper is to classify the cases of alternation of A-V conduction observed in man and to point out the different mechanisms responsible for such alternation.

Alternation of A-V conduction time, in the presence of 1 to 1, A-V response, seems to be restricted to cases with marked P-R prolongation. In such instances, the shorter P-R interval is associated with the shorter R-P distance, suggesting the influence of a *supernormal phase* of conduction.

Where alternation of A-V conduction time occurs with partial A-V response, the alternation can be accounted for by the varying effect of *concealed conduction* of a preceding "blocked" impulse. This is true both for slow atrial rates, namely sinus rhythm with 2 to 1, A-V block, and for very rapid atrial rates, that is flutter with 2 to 1, A-V conduction. A third, and totally different mechanism of alternation of A-V conduction is that of conduction of alternate atrial impulses via different pathways, as seen in the pre-excitation syndrome with alternation of normal and *anomalous conduction*. Examples of each of the 3 varieties are shown to demonstrate the different mechanisms responsible for alternation of A-V conduction time.

**Sensory Nerve Ischemia as Part of the Shoulder-Hand Syndrome**

*H. G. Langford and P. D. Camp, Richmond, Va.*

From 10 to 20 per cent of patients with myocardial infarction develop a syndrome characterized by pain, swelling and limitation of motion of the shoulder and/or hand with, at times, the development of Dupuytrens contracture. The complete pathogenesis of this syndrome remains obscure. Gilliatt showed that in the carpal-tunnel syndrome, the patients developed paresthesias in their fingers much more rapidly, after occlusion of the arterial flow, than did the controls. Evidence was presented to show that this was due to ischemia of the sensory nerves. Marshall showed that in Raynaud's disease, occurring in workers using pneumatic drills, a similar phenomenon occurred.

Twelve patients with shoulder-hand syndrome following myocardial infarction were studied. Two of these had, in addition, early Dupuytrens contracture. One had sensory hypesthesia involving the distribution of the median nerve. The average time to develop paresthesia, after occluding circulation with a sphygmomanometer cuff inflated to 200 mm. Hg, was 29 seconds. The average time for 12 normal controls was 92 seconds. This is a statistically significant difference ($p < .01$) and suggests that ischemia of the sensory nerve is a constant finding in this syndrome. The relation of this finding to the development of the clinical picture is discussed.

**Experimental Miliary Pulmonary Embolism**

*D. Laurent, R. Pick, L. N. Katz, G. Larrain, I. Levinson and H. Gold, Chicago, Ill.*

A series of dogs were injected with a 1 per cent aqueous solution of starch granules via a catheter placed far down the pulmonary artery supplying the lower lobe of one lung. Microscopic examination revealed the starch to be predominantly or exclusively in the injected lobe, which exhibited in each experiment a massive edema 1 hour after embolization. An incomplete infarction developed in most cases. In the untreated unanesthetized dogs this overwhelmingly onesided embolization led to bilateral pulmonary edema, whether or not the pulmonary arterial and wedge pressures rose; general anesthesia (pentobarbital sodium) resulted in less bilateral edema. Sympathicolytic (Benodaïne) and adrenolytic (dibenamine) agents, given prior to the embolization, while only slightly reducing edema formation on the injected side, prevented it in the contralateral lung. A parasympathicolytic agent (atropine) was without effect. The antihistaminic agent, Chlortrimeton, acted like an adrenolytic substance when injected simultaneously with the starch, although it did not reduce the degree of edema in the injected lobe; the action was lessened when the drug was given prior to the starch injection.

Simultaneous measurements of pressures in anesthetized dogs revealed a marked increase in pulmonary arterial pressures and a concomitant or delayed rise in pulmonary venous pressure, while left atrial pressure remained at the control level throughout the whole experiment. The appearance of edema in the noninjected lobes appeared to occur simultaneously with the rise in pulmonary venous pressure. In other experiments, arterial wedge pressure was found to rise pari passu with pulmonary arterial pressure.

These results indicate the contralateral edema formation produced by localized miliary pulmonary embolization cannot be explained exclusively on a hydrostatic basis. Both the increased peripheral pulmonary resistance and the contralateral edema involve some neurohumoral mechanisms. There is suggestive evidence that venoconstriction contributes to the elevation of pulmonary resistance.

**Studies on the Absorption of Colloidal Fat Suspensions by Vascular Cells Growing in Tissue Culture**

*Abel A. Lazzarini, New York, N. Y.*

Studies to elucidate the mechanism of lipid deposition in the arterial wall are usually based on feeding the experimental animal high concentrations of lipids during prolonged periods of time. Many of the difficulties in interpreting these results could be eliminated by in vitro preparations.

Previous attempts made by the author to study this process in vascular cells growing in tissue culture were not feasible because a nontoxic aqueous suspension of cholesterol with a particle size, small enough to enter the cell directly, could not be prepared. A method for the preparation of stable colloidal suspensions of pure cholesterol or animal fat in water or salt solutions without an emulsifier was therefore developed, with a particle size no larger than 250-mμ.

Tissue cultures of adult human aorta and chicken embryo aorta were prepared in a media containing these colloidal suspensions in concentrations of 50 to 250 mg. per cent. Observations under phase contrast microscopy and fixation with osmium tetraoxide and fat staining were carried out periodically. They showed differential absorption of fat, with increasing intraprotoplasmatic droplets and final lateralization of the nucleus. Cells of the subintima had a higher reduction in mitotic index than fibroblasts from the media.

These preliminary investigations suggest histologic differences of fat absorption between cell types of the arterial wall. At the same time, this new approach to the study of the mechanism of lipid cell metabolism may develop into further understanding of the physiopathology of atherosclerosis.

**Epidemiologic Aspects of Acute Myocardial Infarction**

*K. T. Lee and W. A. Thomas, St. Louis, Mo.*

Data pertaining to some epidemiologic aspects of acute myocardial infarction (based on a study of 500 autopsied patients with acute myocardial infarction) have been obtained from a survey of the autopsy and clinical records of Washington University and Barnes Hospital, covering a period of 45 years, from 1910 to 1954, inclusive.

The incidence of acute myocardial infarction in this series was 6.1 per cent in 8,183 autopsies of adults; it is similar to that derived from a smaller series at the Massachusetts General Hospital and is considerably higher than that reported from the Orient and Africa. More data are needed from the latter areas before definitive conclusions can be drawn.

A 20-fold increase in the incidence of acute myocardial infarction has occurred in this autopsy series during the last 45 years. If this reflects a real increase in the incidence of the disease in the population, it suggests that some changing factor in our civilization may be responsible. However, this increase is explained, at least in part, by the changing character of medical care and illustrates the necessity, when analyzing such data from any part of the world, of also taking into account local customs regarding medical care.

When the proportion of males to females in the entire autopsy series is taken into consideration, the incidence of acute myocardial infarction is similar. Reasons for this rather unexpected sex ratio are discussed. The age at which the peak of incidence occurs is at least 10 years later in females than in males. The incidence is significantly higher in white autopsied adult patients (6.4 per cent) than in Negroes (2.9 per cent), and the socio-economic status of the patients in this series does not appear to have been an important factor.

**An Electrophysiologic Explanation of the Electrocardiographic Hypo- and Hyperpotassemia Patterns**

*Eugene Lepeschkin, Burlington, Vt.*

If the ionic theory of A. L. Hodgkin is applied to cardiac muscle, the slowly descending plateau (phase 2) of the trans-membrane action potential would be due to the exit of potassium and the rapidly descending part (phase 3) due to the acceleration of this exit through increase of potassium permeability. The negative after-potential (phase 4) can be ascribed to potassium which has left the cell during phases 2 to 3. The S-T segment corresponds to phase 2, the T wave to phase 3 and the U wave to phase 4. In hypopotassemia, the potassium gradient across the cell membrane increases, phase 2 becomes steeper and the angle between it and phase 3 more obtuse; this explains the typical depression of S-T with diphasic T. As more potassium leaves the cell and is reabsorbed, more will remain outside, causing a greater negative after-potential; this would explain the typical elevation of the U wave. In hyperpotassemia, the gradient is diminished, phase 2 is less steep, the angle between it and phase 3 more acute and the after-potential diminished; this would explain the peaked, elevated T waves and absent U waves. According to this hypothesis, potassium should not influence the total area of the action potential. To test this, the QRSTU area was measured during hypopotassemia and after treatment with potassium, in 5 cases whose heart rate did not change appreciably during treatment. The same method was applied to 5 comparable cases before and after development of hyperpotassemia. The U wave and T wave changes were reciprocal in all cases and the area remained essentially the same.

### Value of Adjusting the Q-T Duration for a Prolonged QRS Complex

*Eugene Lepeschkin, Burlington, Vt.*

In the presence of intraventricular conduction disturbances which cause prolongation of the QRS duration, the total Q-T duration may appear prolonged although the duration of the depolarized state in each section of the ventricle is normal. It was thought that in such cases a better approximation to the true Q-T duration could be obtained by subtracting the difference between the actual QRS duration and the normal QRS duration for a given heart rate from the measured Q-T duration before correcting the latter for the heart rate; the value thus obtained was called the adjusted corrected Q-T duration or Q-Tca. To test this assumption, the QRS and Q-T durations were measured in twenty cases of transient bundle branch block appearing without a considerable change of heart rate, before and after the appearance of the block. It was found that in all cases where the appearance of block was accompanied by complete reversal in the direction of the T waves, the QRS duration and the Q-T duration increased by the same amount, leading to an apparent prolongation of Q-T by 20 to 40 per cent. This was the case in all cases of left bundle branch block and in two of right bundle branch block. In the remaining cases appearance of block was accompanied by a change in the magnitude but not the direction of T; in these cases the Q-T duration increased only by 0.01 to 0.02 second (5 to 10 per cent) or not at all. It is concluded that it is necessary to adjust the Q-T duration for a wide QRS only if the T waves are inverted in leads showing the wide, late R waves.

### A Histopathologic Study of a Case of Complete Heart Block of Forty-Two Years Duration

*Maurice Lev, Julien E. Benjamin and Paul D. White, Miami Beach, Fla.*

This is a histopathologic study of the conduction system in the heart of a 55 year-old woman who, clinically and by ECG study presented evidence of complete heart block for 42 years, or possibly since birth or early childhood. The atriums and ventricles were divided into 16 blocks. These blocks were so fashioned as to include the S-A node, all atrial musculature connecting the S-A to the A-V node, the A-V node and bundle and the left and right bundle branches to the moderator band. Serial sections were cut through the S-A and A-V nodes, A-V bundle and bundle branches. In all other blocks, every eightieth section was retained. In this manner, 14,465 sections were cut and stained.

These sections showed complete obliteration, fibrosis or congenital absence of the A-V node, so that the A-V bundle of His begins in the central fibrous body with no antecedent node. There is absolutely no connection between the atrial musculature and the bundle of His, so that the complete heart block, present clinically, is easily explained. In addition, there were remarkable fibrotic and calcific changes in the atria, with some fibrotic changes in the S-A node. Although the S-A node retains connections with the atrial musculature, the connections are less extensive than normal.

This study shows that a proper correlation of ECG phenomena requires a thorough study of the conduction system. Such a study must involve the S-A node, the approaches to the S-A node and A-V node, the A-V node and bundle, the right and left bundle branches and the atrial and ventricular myocardium.

### Hemodynamic Studies in Five Patients With Heart Block and Slow Ventricular Rates

*David C. Levinson, Lewis Gunther, John P. Meehan, Jr., George C. Griffith and Raymon J. Spritzler, Los Angeles, Calif.*

Five patients (ages 52 to 78) with heart block and findings of arteriosclerotic heart disease were studied by cardiac catheterization. Cardiac failure was not present at the time of study nor at any time previously. Data obtained are recorded.

Simultaneous right atrial and right ventricular pressures were measured with a double lumen cardiac catheter. Atrial pressure waves were recorded in the ventricle and pulmonary artery pulse pressure curves during diastole. A relationship of the height of the right atrial pressure wave to right ventricular contraction was observed. The significant findings are: (1) elevated systolic pressure in the right atrium; (2) elevated systolic pressure in the right ventricular and pulmonary artery; (3) increased pulse pressure in both pulmonary and brachial arteries; (4) increased stroke volume and (5) reduced cardiac output.

The highest atrial systolic pressures were present when atrial systole occurred, immediately after tricuspid valve closure. If atrial systole occurred just prior to ventricular contraction, atrial systolic pressure was elevated, but less than after valve closure. The data collected indicate that there is an increased vascular resistance in both pulmonary and systemic circulations in the patients studied.

### Rauwolfia Serpentina in Treatment of Coronary Artery Disease: Clinical Study of Anginal Syndrome with an Analysis of Methods for Accurate Evaluation of Therapy

*B. I. Lewis, R. I. Lubin, L. E. January and J. B. Wild, Iowa City, Ia.*

Fifteen ambulatory subjects with established angina pectoris were observed for mean periods of 12 months while receiving alternate courses of

*Rauwolfia serpentina* and placebo. We used the double blind technic and, to supplement the clinical evaluations, a modification of the daily report card method. Twelve lead ECGs, two-step exercise tests, ballistocardiograms and teleorentgenograms were obtained on entering the study and at appropriate intervals thereafter.

Initial analysis of the total report card data, to compare results of the combined *Rauwolfia* courses with those of all the placebo periods, disclosed no therapeutic difference between these two agents. The clinical evaluations, however, noted definite improvement in all subjects. Reexamination of individual report card data then revealed a curious sequence of therapeutic events. After an initial placebo period, 9 subjects had distinctly improved on *Rauwolfia*, maintained this during a following placebo period and then improved further with subsequent courses of *Rauwolfia* and placebo. Three others improved with *Rauwolfia* but relapsed on placebo. The remaining 3 did not respond to therapy. This sequential and prolonged therapeutic effect has been noted in other syndromes and extends well beyond the apparent range of *Rauwolfia*'s direct pharmacologic action.

Nine subjects exhibited laboratory changes which correlated, at times strikingly, with therapy. Five abnormal resting ECGs became normal; 4 positive two-step tests became negative; 4 abnormal ballistocardiograms improved or normalized. These changes did not correlate well with the reductions in blood pressure and heart rate. All subjects tolerated *Rauwolfia* well and none developed myocardial infarction during the study.

Our evaluation technics have minimized, but not overcome, the inherent difficulties provided by the very nature of the anginal syndrome and the spontaneous fluctuations in its course. *Rauwolfia serpentina* appears to be an effective adjunct to the management of patients with angina pectoris although its mode of action is unclear.

### Acute Rheumatic Fever in a Large Southern Hospital, 1950 through 1954

*Samuel L. Lieber and Joe F. Holoubek, Shreveport, La.*

Acute rheumatic fever was diagnosed in 162 patients according to criteria established by the Joint report of the British Medical Research Council and the American Heart Association. These patients represent a 5-year mean of 0.59 per cent of the total admissions (27,522) to the combined pediatric and medical wards of a 1000-bed general hospital for the care of indigents. This admission rate of 1 to 163 compares well with that of 1 to 160 at the Charity Hospital in New Orleans for the same 5-year period. Both of these compare well with the admission rate of 1 to 161 at the latter hospital between 1910 and 1925. During this time the ratio at the Massachusetts General Hospital was 1 to 70.

There were 20 white and 142 Negro patients. The great preponderance of Negroes was thought due to their generally lower economic level in this section of the country, plus more crowding, poorer health and greater exposure to group A streptococcal infection. Of the 162 cases, 65 were males and 97 were females. Ages ranged from 3 through 39 years, with a mean of 14. The greatest incidence occurred in the 5 to 14 year age group. There were 92 initial episodes and 70 recurrences. The highest monthly incidence occurred in March and November.

All 9 deaths were associated with intractable cardiac decompensation, and of this group there were 8 Negroes and 1 white person. The incidence of major manifestations was: arthritis 63.6 per cent; carditis 56.2 per cent; chorea 9.3 per cent; subcutaneous nodules 3.1 per cent; erythema marginatum 0.6 per cent. Statistics on age, sex, and race incidence and criteria for diagnosis are compared with other recent surveys.

### Painless Myocardial Infarction in Psychotic Patients

*Arnold L. Lieberman, Northport, N. Y.*

Attention is called to the very large percentage of psychotics suffering variously from an acute abdomen, renal colic, coronary occlusion or ruptured peptic ulcer and who offer little or no subjective complaint of pain. This withdrawal from reality leads to a very large number of severely ill patients, untreated because they are undiagnosed.

For instance patient M. W., age 63, while in the dining room was observed by an aide to cease eating and become very pale. He was transferred to the medical ward. First ECG was normal. Physical examination was completely unrevealing. The patient was, nevertheless, kept for observation. Within 2 days a second ECG revealed a massive anterior infarct which proceeded to go through the usual evolutionary pattern. The typical progress note was: "patient comfortable, no complaints."

Since psychotic patients do not verbalize their pain, many severely ill psychotics are untreated because their organic ailments are undiagnosed.

We agree with Marchand that "we have to depend on alertness of psychiatric aides who live with patients from day to day to call attention of the ward physician to any change whatever of the patients in their charge." When examining a psychotic individual, absence of pain must be taken into account. Whenever the condition objectively points to a coronary occlusion, the lack of pain must not deter one from suspecting the disease.

### The Devolutionary Pattern of Isolated Mitral Stenosis

*William Likoff, Philadelphia, Pa.*

No matter how effectively areas of ignorance obscure the issue, and although occasional individuals

survive the disease over a lifetime, experience attests to a specific devolutionary pattern for mitral stenosis, characterized by a slow maturing of the organic error, a gradual symptomatic expression resulting in incapacitation and death.

To clarify this format of deterioration the clinical patterns of 100 adults with isolated mitral stenosis, confirmed at operation, were selected and the details reviewed from the onset of rheumatic activity until surgical intervention. Ages of the patients ranged from 30 to 60 years and 68 per cent of them were females; in 73 per cent the initial manifestations occurred from 20 to 30 years after the onset of rheumatic activity. Dyspnea and/or hemoptysis were the first symptoms to appear in 55 per cent. The early symptoms were never disabling, and 86 per cent of the patients did not indicate an overt issue as their cause. Pregnancy was the precipitating event in 12 per cent.

During the period of non-disabling symptoms, recurrent rheumatic activity and pregnancy frequently caused incapacitation, but at their termination the patient returned to the initial clinical state.

In 72 per cent of the patients the non-disabling symptoms progressed to produce permanent incapacitation within 10 years.

At surgery, 2 out of every 3 patients had atrial fibrillation and cardiomegaly greater than grade II. Half of the patients in this series had a valve opening a finger tip or less in size and also calcification of the leaflets; 1 out of every 3 had a thrombus in the atrium.

When this data is reduced to a study of averages, a patient with isolated mitral stenosis from rheumatic activity at age 12 will have non-disabling manifestations at 35 and will be seriously incapacitated at 45, at which time cardiac abnormalities will be most severe. Once manifestations occur, they appear to progress inexorably, more as a result of time than from an obvious cause.

### Similarity between the Large Vessel and Forearm "Capillary" Hematocrits as Determined by the Single Circulation Indicator Dilution Technics

*Laurence S. Lilienfield, Renato D. Kovach and Edward D. Freis, Washington, D. C.*

The discrepancy between the large-vessel hematocrit, as measured in Wintrobe tubes, and "total body" hematocrit has not been clarified. Previous studies in this laboratory indicated that the pulmonary-"capillary" hematocrit, as measured by the volumes (Hamilton method) of circulating tagged red blood cells and plasma albumin, closely approximated the large-vessel hematocrit. However, the splanchnic hematocrit, as measured by the volumes (Bradley equilibration method) of splanchnic red blood cells and plasma albumin, was comparable to the total body hematocrit. It was, therefore, of interest to determine the hematocrit of a systemic vascular bed (the forearm), using the indicator washout technic.

A mixture of $Cr^{51}$ tagged red blood cells and $I^{131}$ albumin was injected into the brachial artery. Samples were collected continuously from an antecubital vein. The peak times, mean circulation times and downslopes of $Cr^{51}$ and $I^{131}$ curves revealed that the velocity of the red cells was only slightly greater than albumin. The "capillary hematocrit" was calculated from the formula $H = \frac{R}{K + R}$, ($R$ is the ratio of red cell to plasma mean circulation times; $K$ is the large vessel plasmatocrit divided by large vessel hematocrit). These "capillary hematocrits" were not significantly different from the large vessel hematocrit measured by centrifugation (ratio of capillary hematocrit to large vessel hematocrit is $0.99 \pm .02$ S.D.).

These observations and those previously reported for the pulmonary circulation are difficult to reconcile with currently accepted concepts, as it has been generally assumed that the discrepancy between large-vessel and total-body hematocrits is due primarily to axial streaming in small vessels. Since the capillary hematocrit, as measured by equilibration technics, either for the total body or local vascular areas (splanchnic, pulmonary), is lower than that obtained by the single circulation methods or Wintrobe tubes, it is suggested that the discrepancy is connected in some way with the technic of determination.

### The Post-Commissurotomy Syndrome: Incidence and Clinical Pattern Correlated with the Histochemical Analysis of Atrial Tissue and Serologic Studies

*Philip Lisan, Attilio Reale, T. N. Harris and William Likoff, Philadelphia, Pa.*

The post-commissurotomy syndrome arises after the initial reaction to rheumatic valve surgery has subsided and is characterized by recurrent febrile episodes associated with pleural and/or pericardial pain and effusion, occasionally with alterations in cardiac rhythm or manifestations of congestive failure. Its incidence, etiology, clinical pattern, and specific association with rheumatic heart surgery are open to question.

This investigation is based on a survey of 78 patients, operated on for rheumatic valve disease and 15 operated on for congenital or coronary artery disease; it correlates this syndrome with the new morphologic and histochemical technic of Tedeschi and Wagner for the study of rheumatic activity in the myocardium and also with serial antistreptolysin and antihyaluronidase titers, blood profiles and cultures, chest x-ray films and electrocardiograms.

The syndrome occurred in 18 per cent of the patients who had valve surgery but was not observed in any of the control group. It was three times more

common after isolated mitral than after aortic or combined valve surgery. Atrial biopsy of 12 of the 14 patients with the syndrome indicated chronic nonspecific carditis and failed to disclose Aschoff's nodules. No instance of an exudative Aschoff nodule or chronic recurrent carditis was observed. The serologic studies were normal in all these patients. The atrial biopsy was negative for exudative reaction in one patient with unmistakable rheumatic reactivity in whom a sharp rise in serologic studies was recorded. Examples of a variety of postoperative complications, superficially simulating a post-commissurotomy syndrome, are discussed and illustrated.

It appears from this data that the syndrome is specific in its clinical picture and is not accompanied by alterations in the serologic studies for recent streptococcal infection. Atrial biopsies do not reveal continuing rheumatic activity in patients who develop the syndrome, but this was also true when actual rheumatic reactivation occurred.

**Resonance of Pulsating Fluids**

*Harry Lobel, Omaha, Neb.*

Circulation is subject to two types of laws, laws of hydraulics and of resonance. These laws must be studied separately. To separate the effects of these two types of laws, pulsations are produced in tubes of fluid. At the proper frequency the pulsations become resonant or tuned. The effect of changes in elasticity upon resonance are then studied. Interpreted through the concepts of dynamic engineering, the theory of resonance applies to the pulse waves of the circulatory system in the same sense that it applies to the sound waves of a pipeorgan or to the mechanical vibrations of a machine.

A lineal flow superimposed upon pulsations produces pulsating flow. The effect of pulsations upon lineal flow is analyzed. The measured pulsating flow corresponds to the theoretic pulsating flow by over 90 per cent. Impedance is a serious problem in dynamic engineering. In a machine which is out of resonance, it causes loss of efficiency, vibrations, fatigue of metal, excessive wear of bearings and breakdown. Impedance is readily demonstrated in a pulsating hydraulic system which is out of tune. It produces loss of efficiency, excessive pressure, increased impact on the conduit and strain on the pump.

There are indications that the circulatory system is a resonant or tuned system and that this system can be thrown "out of tune." Could a pathologic change in the structure of the aorta throw this system out of tune? Could this produce impedance? Could tuning be a factor in the impedance of the vessels in hypertension?

**Patent Ductus Arteriosus with Reversal of Flow**

*Frank London, T. D. Stevenson, A. G. Morrow and J. A. Haller, Bethesda, Md.*

An increasing number of clinical reports indicate that the syndrome of patent ductus arteriosus with reversal of flow is not rare. Three such patients have been studied clinically, by cardiac catheterization, angiocardiography, retrograde aortic catheterization, aortography and by the use of Priscoline and inspired air mixtures containing high and low oxygen concentration. These studies showed normal pulmonary "wedge" pressures, increased pulmonary vascular resistance, pulmonary hypertension to a level equal to the pressure in the systemic circuit and right ventricular hypertension. Right brachial artery oxygen saturation was higher than the femoral artery oxygen saturation in each patient. One patient showed marked right brachial arterial oxygen desaturation. Arterial blood in the region of the sinus of Valsalva was also desaturated. Inhalation of 100 per cent oxygen did not produce complete saturation of this patient's blood but Priscoline administration significantly improved the saturation. This patient had an interventricular defect in addition to the ductus.

The clinical difficulty in separating this entity from the Eisenmenger syndrome, primary and past embolic pulmonary hypertension, aortic septal defect with pulmonary hypertension and atrial defect with pulmonary hypertension is stressed. The physiologic methods useful in differentiating these entities are discussed. Two of these patients were operated on in an attempt to close the ductus and both died as a result of hemorrhage from the pulmonary artery. A brief review of 47 documented cases from the available literature with their course and operative results are presented.

**The Clinical Behavior and Operative Management of Popliteal Aneurysms**

*Jere W. Lord, Jr., New York, N. Y.*

The commonest cause of popliteal aneurysms is a weakening of the wall of the artery by atherosclerosis. Other less common causes are trauma, syphilis and bacteremic infections.

Although the pulsating mass may be asymptomatic in some instances, one or more of the following complications may occur. (1) Pressure on the adjacent popliteal vein will lead to edema of the lower leg and occasionally to a frank thrombosis of the vein. (2) Thrombosis of the aneurysm, with cessation of arterial flow through the main artery and impairment of the collateral arterial flow by pressure from the aneurysm, may result in gangrene of the foot. (3) Embolic occlusion of the smaller arteries in the leg by pieces of the everpresent thrombotic material in the aneurysmal sac may lead to gangrene of the foot or toes. (4) Pain in the leg may

be due to pressure on the tibial and peroneal nerves. (5) Acute rupture of the aneurysm may threaten the entire limb and jeopardize the patient's life.

Although the popliteal aneurysm may be associated with aneurysms elsewhere in the arterial system, the most frequent site for a second aneurysm is in the other popliteal artery. Because the incidence of complications is high, popliteal aneurysms should be treated surgically when diagnosed, unless a strong contraindication exists. There are two excellent operations available, one simple and conservative, the other more difficult and radical. Each patient should be individually studied in order to determine the appropriate procedure. The conservative one is the time-honored obliterative endoaneurysmorrhaphy of Matas. In some patients, a preliminary, complementary or supplementary lumbar sympathectomy is advisable. The radical operation consists of total excision of the aneurysm and insertion of a graft, either of the autologous vein or of the homologous arterial, between the ends of the artery. Twelve popliteal aneurysms have been operated upon by the two methods and all patients have intact and usable extremities.

**The Patterns of Pressure Pulses Obtained Through Cardiac Catheterization in the Normal Heart and in Clinical Conditions**

*A. A. Luisada, C. K. Liu, and E. Jona, Chicago, Ill.*

An improved method of obtaining pressure pulse from the heart and vessels was successfully employed. It is based on the use of photographic recording, high speed film, full utilization of the amplifying power of an electromanometer and simultaneous tracing of a phonocardiogram. With this method, tracings of the superior and inferior venae cavae, right atrium, right ventricle, pulmonary artery, and "wedged" pulmonary tracings, were recorded in the normal man and in the normal, anesthetized dog.

Simultaneous pressure tracings and electrokymograms of the same chambers were recorded in some. Analysis of the normal pressure pulses was made through comparison with sound and kymographic tracings.

The same study was repeated in these clinical cases: (1) in atrial septal defects; (2) in ventricular septal defects; (3) in mitral stenosis before and after commissurotomy; (4) in chronic cor pulmonale and in (5) complex congenital malformations.

In addition to the tracing of the left atrium (atrial shunts), these observations permitted the recognition of a special right atrial pattern in atrial defects and of various right ventricular patterns in various conditions of right ventricular overload. The possible diagnostic value of the pulmonary "capillary" tracing for recognition of mitral insufficiency is discussed.

**Lipoproteins and Diet in Coronary Heart Disease: A Five Year Study**

*Thomas P. Lyon, Alexander Yankley, John W. Gofman and Beverly Strisower, Berkeley, Calif.*

A follow-up study over the past 5 years of 351 patients with myocardial infarction and 119 patients with angina pectoris has shown (1) that the previously reported lipoprotein atherogenic index elevation in coronary heart disease is confirmed in this study; (2) The prognosis in angina pectoris is strikingly and significantly worse when the lipoprotein atherogenic index is high. (3) In a series of 351 patients with myocardial infarction, those who died in the follow-up period showed significantly higher atherogenic index values than those who survived; (4) The lipoprotein atherogenic index measure is much superior to the serum cholesterol measurement as an indicator of the lipid disorder in coronary disease; (5) The low fat, low cholesterol diet is effective in maintaining chronically lowered lipoprotein atherogenic index values; (6) Coronary patients not following a low fat, low cholesterol diet showed 4 times as great a recurrence and death rate as shown by those patients who did adhere to the low fat, low cholesterol diet; (7) Thyroid hormone and heparin reduce certain segments of the lipoprotein spectrum and, in addition, heparin in certain cases of coronary disease produces ECG reversion toward normal.

**Baroceptor Function in Experimental Renal Hypertension**

*J. W. McCubbin, J. H. Green and Irvine H. Page, Cleveland, O.*

The buffer reflexes fail to prevent chronic hypertension possibly because (1) the depressor effect of even maximal baroceptor discharge may be overwhelmed by a stronger pressor mechanism; (2) baroceptors may fire submaximally, by adapting to the higher pressure levels and (3), baroceptors may be destroyed, either completely or in part. These possibilities were examined in 3 sets of experiments on dogs.

At first, one common carotid artery was exteriorized in a skin flap and both aortic depressor nerves and the contralateral carotid sinus nerve were cut. Arterial pressure response to carotid clipping was measured weekly without anesthesia before, during and after development of cellophane perinephritic hypertension. These responses were found to persist and were somewhat enhanced during the chronic phase of hypertension, indicating, in accord with other studies using anesthetized animals, that baroceptors are not destroyed. Secondly, electroneurograms of single and multifiber preparations of sinus and aortic nerves showed that the pattern of firing in hypertensive dogs is discontinuous and similar to that in normotensive animals. Exact comparison of patterns between normotensive

and hypertensive animals was prevented by differences in mean and pulse pressures from animal to animal, necessitating the third group of experiments.

One carotid sinus of normotensive and chronic renal hypertensive dogs was vascularly isolated and standardized and reproducible pressure wave forms were applied by a perfusion pump, while action potentials were recorded from single and multifiber preparations of the sinus nerve. The pattern of these responses in renal hypertensive dogs, when compared with those of normal dogs, are consistent with an altered, higher "set" of baroceptor function. Baroceptor discharge commenced at higher pressure levels in renal hypertensive animals and, unlike that in normotensive animals, was not steady at severely hypertensive levels.

**Pathogenesis of the Lower Leg Syndrome: A Study of the Phlebodynamics of the Lower Extremity**

*H. D. McIntosh, S. C. Fell, A. T. Hornsby and J. V. Warren, Durham, N. C.*

The function of venous valves of the lower extremity was studied by correlating roentgenologic observations with pressure measurements in 15 normal subjects and 10 patients with chronic leg ulcers. Femoral, saphenous and popliteal pressures were recorded simultaneously by strain gages; recordings, therefore, were obtained both above and below valves.

During quiet standing, the column of blood from the foot to the heart in normal and pathologic extremities is uninterrupted, the valves being held open by the heartward flow of blood.

Reversal of the venous pressure gradient by the Valsalva maneuver instantly closed the valves in normal subjects. The femoral pressure rose rapidly to equal the increased intra-abdominal pressure; popliteal pressure gradually rose by a similar increment, at which time it was apparent from pressure contours that the valves between these 2 points were open. Despite prolonged straining, saphenous pressure never equaled the rise of femoral and popliteal pressures, for the communicating veins did not permit retrograde transmission and superficial flow was insufficient to raise the pressure to equal that of the deep system. Contrariwise, in patients with chronic leg ulcers, pressure changes due to straining were transmitted directly to the saphenous vein. Tortuous, dilated communicating veins were demonstrated radiographically. These subjects had incompetency of valves as well as communicating veins. Similar studies were carried out during cough, ambulation and other maneuvers.

These observations suggest that the venous system in the leg is divided, by valved communicating veins, into two compartments the deep and superficial. In addition, competent valves protect the more distal veins from sudden changes of intra-abdominal pressure and, during muscular activity, segmentalize the system. Destruction, or alteration of valves and communicating veins, permits undiminished transmission of increased pressure, with cough often reaching 300 mm. Hg, to superficial vessels, poorly supported by tissue pressure. These abnormal pressure rises may contribute to edema formation and chronic leg ulcers.

**Spectral Phonocardiography: Current Status as a Research, Clinical and Teaching Tool**

*Victor A. McKusick, Baltimore, Md.*

Spectral phonocardiography (Bell sound spectrography, "visible speech," adapted to the study of cardiovascular sound) records, analyzes and displays heart sounds and murmurs in 3 dimensions: time is the abscissa and frequency scale the ordinate; intensity is displayed as density.

Advantages of the method result mainly from the spreading out of frequency: (1) resolution in the time dimension is improved since splitting of heart sounds, for example, if not apparent at all frequencies, is likely to be detectable at some; (2) timbre is displayed and given physical definition; hemodynamic basis for variations in the musicality of murmurs has been investigated; (3) the wide dynamic range of cardiovascular sound is more nearly encompassed, for example, a very loud systolic murmur and a very faint diastolic murmur can be presented in one record in approximately their true intensity proportions; (4) being detailed recordings of the 3 parameters of sound, these recordings look the way the heart sounds, an advantage in teaching and in communication of auditory findings; (5) artefacts in the form of non-cardiovascular noise, arising inside or outside the body, can usually be recognized as such and disregarded in the heart sound analysis.

A spectral phonocardiograph of new design has the following features: (1) only one magnetic recording step for improved preservation of intensity; (2) a filter system optimum for cardiovascular sound; (3) oscilloscopic display for facility in stretching the time dimension by merely changing sweep speed; (4) photographic recording for improved depth of density display.

An experiment in the teaching of clinical auscultation was conducted. Half of the class was taught by means of tape recordings of heart sounds; the other half, in addition, viewed the spectral phonocardiogram of the same segment of sound. These visual displays should be useful in bridging the gap between the verbal description and what is heard with the stethoscope.

**Congenital Anomalies of the Mitral Valve**

*Dan G. McNamara, Earl F. Beard and Harvey S. Rosenberg, Houston, Tex.*

The clinical, physiologic and anatomic features of congenital deformities of the mitral valve are re-

viewed as seen in six cases, all confirmed by autopsy. All patients except one died under the age of one year.

Two cases of isolated congenital mitral stenosis were characterized by early congestive failure, absence of cyanosis, right ventricular hypertrophy, signs of pulmonary arterial hypertension and left atrial enlargement. Murmurs were variable and not characteristic as in acquired mitral stenosis.

A case of *cor triatriatum* (or stenosis of the common pulmonary vein) was functionally similar to congenital mitral stenosis and showed similar clinical features. Pulmonary arterial and pulmonary capillary pressures were elevated at cardiac catheterization in both of these lesions. Such pressure elevation in acyanotic congenital heart disease, seen with the clinical signs mentioned and in the absence of an intracardiac shunt should suggest a congenital stenotic lesion of the mitral valve.

Congenital atresia of the mitral valve in 3 cases, all verified by autopsy, showed clinical findings which varied with the other cardiac malformations present. An atrial septal defect, with left to right shunting of blood, was present in all cases, and the aorta arose from the right ventricle in all cases, allowing shunting of unoxygenated blood into the systemic circulation. While the peripheral arterial blood must be partially unoxygenated in this lesion, the degree of cyanosis varied. Of 2 cases with profound cyanosis, 1 was complicated by pulmonary artery atresia and one by single ventricle with transposition of the great vessels. All 3 cases showed X-ray evidence of increased pulmonary vascular markings and of left atrial enlargement. Death occurred under the age of 3 months in each instance.

**Adrenal Insufficiency in Patients with Myocardial Infarction and Shock**

*Benjamin Manchester, Washington, D. C.*

On rare occasions one may encounter shock, secondary to myocardial infarction, that resists all form of therapy. The consideration, that vasomotor collapse may in itself perpetuate the shock-like state by interfering with homeostasis and the restoration of normal vasomotor tone, is not often appreciated. Under such circumstances, adrenal failure may be the result or the cause of prolonged shock.

Seven subjects with acute myocardial infarction and severe shock that failed to respond to vasopressor drugs, oxygen and the usual supportive measures are the subject of this study. Shock persisted for 8 to 34 days. Twenty-four hour urine ketosteroid determinations and total eosinophil counts taken on 3 consecutive days, indicated adrenal insufficiency.

Norepinephrine, in a dosage of 64 mg. for 24 hours, was ineffective in maintaining a systolic blood pressure of 110 or higher. The administration of hydrocortisone and desoxycorticosteroid, together with an adequate amount of sodium and norepinephrine, resulted in dramatic vasomotor response, not observed prior to adrenal steroid administration. Potentiation of norepinephrine by adrenal steroids resulted in lower doses, needed for vasopressor medication. The one patient who did not receive this form of treatment died, despite the vigorous use of vasopressor medication. Necropsy revealed a lung abscess, the congenital absence of the left and total necrosis of the right adrenal gland, as well as bacteremia and myocarditis. The remaining 6 patients recovered and did not require supplemental adrenal steroid or vasopressor medication. Subsequent studies, after recovery, demonstrated that these 6 patients had normal adrenal function.

Prolonged shock and the stress of myocardial infarction may produce adrenocortical failure. If unrecognized, vasopressor therapy alone would be inadequate to correct the shock.

**Value of Long Term Anticoagulant Therapy in Myocardial Infarction**

*Benjamin Manchester, Washington, D. C.*

There were 506 patients in this study of myocardial infarction. Of these, 206 patients served as as controls. Of the test patients, 147 had been on anticoagulant therapy for a period of 1 to 8 years. The patients were observed for immediate mortality, thromboembolic complications and the effect of anticoagulants. The value of long term anticoagulant therapy upon the incidence of congestive heart failure, angina pectoris and longevity was also noted.

It was impossible to properly evaluate patients with myocardial infarction as "good" and "poor risks" at 24-hour intervals for the initial 120 hours. Of the "good risk" patients, 25 per cent shifted into the "poor risk" category, while one third of the "poor risk" patients had an uneventful convalescence.

The mortality rate for the anticoagulant-treated and the control groups was 10 per cent and 19 per cent respectively. Thromboembolic complications occurred in 5 per cent of the patients treated with anticoagulants and in 18 per cent of the control group. The incidence of angina pectoris was essentially the same for both groups. Thirty per cent of the patients, classified as "poor risks" and treated with anticoagulants, developed heart failure, whereas 50 per cent of the comparable control group showed signs of failure.

The advantages of prolonged anticoagulant therapy in patients with myocardial infarction are unknown. This study seems to indicate that continuous anticoagulant therapy for at least one year, in patients with previous infarction, may increase the chance of survival and reduce the incidence of thromboembolic complications and congestive heart failure.

**Lateral Plane Ballistocardiography: Its Clinical Importance**

*Harry Mandelbaum and Robert A. Mandelbaum, New York, N. Y.*

It is unwise to base conclusions on the effect of aging, disease or drugs upon abnormal head to foot BCGs, unless studies in the lateral plane show that these aberrations are not directional. The Dock platform BCG is mounted on stiff springs. This is placed under the upper 15 inches of the thorax and shoulders of the subject, and, in this position, records only the lateral forces. A similar platform BCG is placed under the hips, at right angles to the other instrument and this records the head-foot forces. These are recorded simultaneously on a 2-channel ECG a synchronous radial pulse trace serves for timing.

In normal young subjects, with rightward forces causing upward galvanometer deflections, the complexes show deflections one-fourth to one-half as great as the head-foot waves. H and I are prominent, K is small, and the diastolic waves are usually equal to or are slightly more prominent than the J waves of the lateral plane BCG. In older subjects and in advanced hypertensives, low amplitude head-foot systolic waves may have reciprocal large amplitude complexes in the lateral plane. This should be regarded as a directional effect, and may be due to a shift in the axis of left ventricular ejection on expiration.

In coronary artery disease, indefinitive lateral traces parallel the deterioration observed in the head to foot records. The diastolic complexes in the lateral trace may provide the first indication of high atrial pressure. These may be striking in constrictive pericarditis, congestive heart failure and mitral valve disease, even when the head to foot trace reveals no significant diastolic waves.

**The Measurement of Liver Circulation in Burn Patients by Means of the Colloid Disappearance Rate**

*Paul Mandelstam, Harry S. Soroff and Ernest L. Dobson, Fort Sam Houston, Tex.*

Studies of hepatic circulation in burn patients were carried out by measurement of the rate of disappearance from the blood stream of colloidal chromic phosphate labelled with $P^{32}$, by a method previously described. (E. L. D.) Inasmuch as the colloid removal from the blood stream is carried out almost exclusively in the liver and spleen, the disappearance rate constant represents the minimal fraction of the total blood volume perfusing the liver per unit time. Plasma volume was simultaneously measured with Evans Blue dye (T-1824). Total blood volume was computed from the plasma volume and hematocrit. The blood volume traversing the liver per minute was calculated by multiplying the total blood volume by the disappearance constant of the radioactively labelled colloid.

Nine patients, with mean full thickness burn of 23 per cent and mean total extent burn of 46 per cent, were studied at postburn intervals varying from 4 to 79 days. In no patient was there hypotension, oliguria or any other clinical evidence of shock at the time of study. Six of these nine patients succumbed, at varying intervals after study, all in association with septicemia.

In these nine patients, the mean disappearance constant was 0.595, in constrast to a mean of 0.282 found by one of us (E. L. D.) in 29 normal males. Correspondingly, the mean half-time in these patients was 1.58 minutes, as compared to a mean of 2.50 minutes in the 29 normal subjects. In all patients, the total blood volume was, in terms of the patients' preburn weights, normal or above.

Three patients, who had incurred extensive burns 6 to 9 months previously and who were in good health at the time of study, exhibited disappearance constants and half-times within normal limits.

It is concluded that in extensively and deeply burned patients there is a very substantial increase in hepatic blood flow until skin coverage is achieved and convalescence well underway. Simultaneous cardiac output and hepatic blood flow studies are now being performed in order to determine whether or not the increased hepatic blood flow is solely a reflection of an increase in cardiac output.

**Plasma Concentration of Epinephrine and Norepinephrine in Hypertension**

*William M. Manger, Jesse L. Bollman, Khalil G. Wakim, Joseph E. Berkson, Edward J. Baldes and Grace M. Roth, Rochester, Minn.*

For the quantitation of epinephrine and norepinephrine in the plasma of patients with hypertension and in experimental hypertension in the dog, the fluorometric method of Weil-Malherbe and Bone, with some modification, was used.

In healthy men and women the highest concentration of epinephrinelike substance per liter of plasma was 3.6 μg. In more than 90 per cent of an equally large number of patients with essential hypertension, the concentration of epinephrinelike substance was less than 3.6 μg per liter of plasma; yet several of these patients occasionally had concentrations of from 4 to 5 μg. In 21 patients with pheochromocytomas, the concentration of epinephrinelike substance was invariably greater than 4 μg per liter of plasma when the hypertension was sustained or when blood was drawn during a paroxysmal episode of hypertension. However, persons exhibiting a hyperreactive blood pressure response to the cold pressor test or having paroxysmal hypertension without pheochromocytoma so far have been found to have normal plasma concentrations of pressor amines. Patients with Cushing's

or Graves's disease with hypertension have had normal concentrations of epinephrinelike substance in the plasma; whereas in some patients with hypertension associated with increased intracranial pressure, or periarteritis nodosa or chronic glomerulonephritis (particularly with severe azotemia), the concentration of epinephrinelike substance per liter of plasma has been elevated above 4 μg. In the presence of severe azotemia, either clinically or experimentally, the fluorescent substance measured by the procedure of Weil-Malherbe and Bone may not be entirely epinephrine and norepinephrine. The concentration of pressor amines was not significantly elevated in 2 patients who had mild toxemia of pregnancy and hypertension.

Hypertension induced in the dog by asphyxia, or increased intracranial pressure, or electrical stimulation of sympathetic nerves, was accompanied by a significant increase in the concentration of pressor amines in the plasma. Induction of hypertension in two dogs by wrapping their kidneys with cellophane caused no significant change in the concentration of pressor amines.

**Experiences of a Heart Station Doing Cardiac Catherizations and Angiocardiography in a Private Hospital: a Two Year Report**

*Harold Margulies and John Gustafson, Des Moines Ia.*

A diagnostic heart station was established with private funds in a private hospital. The method of organization and administration have been vital to its success and is described. In the first 2 years there were approximately 50 cardiac catheterizations with 1 death due to ventricular fibrillation, 30 venous angiocardiograms with no deaths, and 6 retrograde aortograms with 1 death. The fatality is briefly described.

Patients are screened through a cardiac clinic and seen by every member of the heart station; group decision is used to select procedures which may be hazardous. The heart station is now well established and has made possible successful surgery including repair of ventricular septal defects at another institution. The kinds of abnormalities suspected and proven are described.

**Acyanotic Cardiac Lesions with Continuous Murmurs Simulating Patent Ductus Arteriosus**

*Herbert Mark and Dennison Young, New York, N. Y.*

A continuous machinery murmur heard in the second interspace to the left of the sternum is generally considered pathognomonic of patent ductus arteriosus (PDA). A number of acquired and congenital acyanotic cardiac lesions, however, are also associated with similar murmurs. While these lesions are rare, they should be considered in the differential diagnosis because a PDA is almost uniformly amenable to surgery while mimicking lesions are for the most part not yet surgically approachable.

During the past 5 years we have observed a group of patients, each with continuous murmurs heard at the base of the heart, suggesting to at least one qualified observer a PDA. Cases of interventricular septal defect, aortic septal defect, acquired aorticopulmonary artery fistula, acute rheumatic carditis, rheumatic heart disease associated with kyphoscoliosis and congenital aortic valvular lesion were evaluated. Subsequent diagnostic studies, autopsy, or surgery served to eliminate the diagnosis of PDA in these cases.

Additional observations from the literature on lesions that have been confused with patent ductus arteriosus because of the presence of continuous murmurs are included. This group consists of ruptured aneurysms of the sinus of Valsalva, aortic-caval fistula, arteriovenous aneurysm on the pulmonary artery, arteriovenous fistula of the wall of the left ventricle and pulmonic stenosis.

It appears that the continuous murmur, although originating along the left sternal border in each instance, was heard maximally in an area other than the second left interspace and the distribution of the murmurs was more widespread than that usually present with a patent ductus. Fairly distinct localization of the continuous murmur to the second left interspace with maximal transmission towards the left shoulder is the most important clinical finding in PDA unless this is associated with another anomaly. The commonest associated anomaly in our experience has been congenital aortic valvular disease.

**The Blood Pressure in "Hypertensive Heart Disease" in People over Sixty-five**

*Arthur M. Master, Richard P. Lasser and Harry L. Jaffe, New York, N. Y.*

A study of blood pressure in people over 65 was conducted by means of questionnaires sent to internists and general practitioners throughout the country. Five hundred cases were singled out for further investigation in which the physician had made a diagnosis of hypertensive heart disease. A follow-up letter was sent out to obtain the specific basis for the diagnosis, i.e., the presence of angina pectoris, enlargement of left ventricle, ECG abnormalities, cerebrovascular accident or congestive heart failure.

Information was thus obtained as to what was termed hypertensive heart disease by the practicing physician and the incidence of the various cardiac abnormalities enumerated was determined. The blood pressure data were analyzed for the average, the range, and the frequency distribution

according to age and sex. The effect of each type of cardiac complication on the blood pressure was evaluated. The results in this series of patients with heart disease were compared with those found in normal persons over 65 years of age.

### Idiopathic Cardiac Hypertrophy

*J. B. Masters and John H. Woodbridge, Northridge, Calif.*

Cardiomegaly is not an uncommon finding at autopsy. In the majority of instances, the enlarged heart is due to a familiar organic disease process. Approximately 15 per cent are cases of massive cardiac hypertrophy due to some unknown cause and these have been classed by pathologists as idiopathic cardiac hypertrophy. Fewer than 100 proven cases have been found in the literature. Four new case reports, including autopsy findings and microscopic descriptions, are presented here in detail.

The kindredship of this disorder to endocardial fibroelastosis has received much speculative attention. Nutritional and exertional factors and some infectious diseases have been linked with this disorder, a racial or familial factor has been suggested. Ninety-five per cent of reported cases have been adults, 80 per cent occurred in males. The illness is characterized by recurrent bouts of increasingly severe congestive failure, various arrhythmias occur, gallop rhythm is frequent, pulmonary emboli and infarcted viscera are common, mural thrombi are demonstrated frequently, murmurs are not characteristic. Heart valves are normal. Moderate leucocytosis, fever and abnormal ECGs with frequent bundle branch block abnormalities are demonstrated; chest x-ray films reveal a massive heart, enlarged in all diameters. Pathologically, myocardial hypertrophy with increase in fiber size, hyperchromatism and altered shape of nuclei are seen. There are insignificant increases in the stroma, minimal necrosis, minimal perivascular cellular infiltrations, minimal endocardial fibrosis and minimal pericardial scarring, but there are no valvular lesions.

The authors believe that idiopathic cardiac hypertrophy is a specific disorder in which the primary etiology may be linked with a condition of endocardial and myocardial anoxia, probably due to a congenital obliterative process in the subendocardial circulation. In search for the cause, further attention should be directed to the myocardial cellular physiology. With a high index of suspicion, the antemortem diagnosis can be made. This will lead to a better understanding of the disorder as a clinical entity.

### Standardized Clotting Time in the Control of Dicumarol Therapy

*George A. Mayer, Kingston, Ontario, Canada*

Experts agree that the Quick one-stage prothrombin test affords less than ideal control of oral anticoagulant therapy. It is widely used because no adequate simple substitute has been proposed.

The author has developed a standardized clotting time test. It utilizes unmodified venous blood in uncoated capillary glass tubes under constant temperature conditions. The technic is simple and requires no special reagents, expensive apparatus or special training. The readings are expressed uniformly in absolute terms, easily comparable in different reports. Normal values for healthy male adults are 9.85 minutes (S.D. $\pm$ 0.72 minute). The standard error of the technic is $\pm 2$ to 4 per cent. The arbitrary therapeutic range during oral anticoagulant therapy is from 15 to 20 minutes. Data are presented contrasting this control with the Quick one-stage prothrombin test, during the treatment of 40 patients with Dicumarol.

While the curves of the two tests during the period of observation are reasonably parallel, adequate clotting time prolongation was obtained at widely varying prothrombin levels. Further, a consistent lag in reaching adequate clotting time was noted. The average time to attain 30 per cent prothrombin activity was 3.3 days and for 15 minutes clotting time, 4.9 days.

In the higher therapeutic ranges, there was an important discrepancy. During 98 treatment days when the prothrombin activity was between 10 and 20 per cent, clotting time was over 20 minutes on only 47 occasions; on 16 days when prothrombin activity was less than 10 per cent, clotting time was unduly prolonged on only 5 occasions. The clotting time has proven a satisfactory technic for the control of anticoagulant therapy in these cases, and seems to possess important advantages over the Quick one-stage prothrombin test.

### The Physical Work of the Digital Blood Vessels in Hypertension

*Milton Mendlowitz, Albert D. Parets, Theodore Gold and Stanley R. Drachman, New York, N. Y.*

In 23 normotensive and 36 hypertensive subjects, digital flow-pressure ratios were measured at room temperature varying from 25.5 to 29 C. and after inhibition of the sympathetic nerve were discharged by indirect heat supplemented by 0.8 mg. per Kg. of SC 1950, administered intravenously. Work of vasoconstriction was calculated from the formula $\frac{\pi}{4l}(r_1^2 - r_2^2)(P_1 + P_2)$ in which $r_2$ is the radius equivalent in cm. during vasocon-

striction. This is corrected for estimated changes in the pressure axis intercept of the flow-pressure slope, a factor including changes in apparent viscosity and in critical closing pressure produced by vasoconstriction. The accuracy of this estimation was tested in 3 normotensive and 3 hypertensive subjects. When $r_1$ is the radius equivalent after vasodilatation in cm., $P_2$ is the mean arterial pressure during vasoconstriction, and $P_1$, the mean arterial pressure after vasodilatation, each minus venous pressure and in dynes per cm.$^2$; $l$ is the estimated length in cm. of the theoretic single tube equivalent of the digital vascular bed. The work index or the percentage of the potential work at any intrinsic caliber and pressure, represented by the actual work of vasoconstriction, was calculated from the formula $\frac{100(r_1^2 - r_2^2)(P_1 + P_2)}{r_1^2(P_1 + P_m)}$ in which $P_m$ is the closing pressure for maximal vasoconstriction.

The work of digital vasoconstriction and the percentage work index, estimated in this way, are significantly greater in hypertensive than in normotensive subjects. Also, the decreased intrinsic caliber of the digital blood vessels in hypertensive subjects, as measured during vasodilatation, is not caused by contraction of vascular smooth muscle, but probably by either sclerosis or edema of the arteriolar walls or both.

**Effect of Anoxia on the Glutamic Oxalacetic Transaminase Content of the Myocardium of the Rat**

*Joseph M. Merrill, Janet Lemley-Stone and George R. Meneely, Nashville, Tenn.*

Ischemic necrosis causes a large decrease in the serum glutamic oxalacetic transaminase (SGO-T) activity of myocardial tissue. Since anoxia produces profound alterations in myocardial metabolism, experiments were conducted to determine the effect of anoxia on the concentration of glutamic oxalacetic transaminase in myocardium and serum. The mean concentration of SGO-T in the myocardium of normal male albino rats was 530 ± 20 (S.E.) units per mg. of wet tissue (2304 units per mg., dry).

Experimental rats were subjected to acute anoxia for 1 hour by a low-pressure atmosphere equivalent to 7 per cent oxygen. Respiratory arrest was then induced by further decrease to a pressure equivalent to 3 per cent oxygen. Blood was immediately obtained from the inferior vena cava for serum analysis, the heart was removed and the ventricular mass assayed for enzyme activity.

The mean concentration of SGO-T in anoxic myocardial tissues was 389 ± 18.4 units per mg. of wet tissue (1852 units per mg., dry). This 27 per cent decrease from control levels was statistically highly significant (P = 0.001). The hepatic tissues of anoxic rats also showed a decrement of SGO-T activity. The decreased tissue concentration of enzyme was not accompanied by elevated serum activity.

These results indicate the relationship between serum and tissue enzyme concentration is different in myocardial anoxia and ischemic necrosis. Whereas, in experimental myocardial ischemic necrosis, the loss of enzyme from the myocardium is reflected by a proportional rise in serum enzyme concentration, this did not occur following experimental anoxia. This suggests local destruction of myocardial transaminase, although diminished production or transport away from the myocardium, at undetectably low blood levels, are alternative possibilities.

**Ten Year Follow-up of Malignant Hypertension Treated by Sympathectomy**

*William J. Messinger, New York, N. Y.*

Ten years have elapsed since our initial study of patients with hypertension. A group designated as having "malignant hypertension" was previously reported by us. We are now reporting our results in a group of 26 patients subjected to sympathectomy. A group of 31 patients, not subjected to operative procedures, has been followed-up as a control group for the past 10 years.

At the time of this study, drugs for the control of hypertension were only in their formative periods and operative intervention appeared to be worthy of trial. Twenty-six patients consented to the surgical procedure and the remainder served as a control group.

The persistence and range of blood pressure in our patients was observed over a sufficient period of time to rule out anxiety states, metabolic disturbances and hypertension of known endocrine origin. Standard clinical methods for evaluation of renal function were used. In some instances the histamine test and perirenal air insufflation studies were used as supplementary procedures when indicated. Range of blood pressure as a measure of the reactivity of the sympathetic nervous system was determined by the use of the cold pressor test and sodium amytal sedation; in some patients with angina, the standard Master's two-step test was used. The Smithwick Procedure was used, modified in a few instances to include thoracic ganglia 1 to 3 for patients with angina. This report represents observations over a ten year period of both the operative group and the control group.

In the operative group, half of the patients were alive at the end of 5 years and 1 after 10 years. In the control group, all were dead at two and a quarter years. Necropsies obtained in 17 of our 26 operative patients indicated correct diagnosis in 15.

Of the 2 errors in diagnosis, 1 patient had a functioning pheochromocytoma and the other had chronic nephritis. In the control group, 14 necropsies were performed, and one of these patients should have been diagnosed as having chronic nephritis.

**Pathogenesis of Cardiovascular Abnormalities in Fetal Rats Following Transitory Maternal Pteroylglutamic Acid Deficiency**

*I. W. Monie, M. M. Nelson, C. D. C. Baird and H. M. Evans, Berkeley, Calif.*

Congenital cardiovascular abnormalities have been produced in the offspring of rats maintained on a diet deficient in pteroylglutamic acid (PGA) for 2 to 3 days in the early part of pregnancy. The pathogenesis of many of these abnormalities has been observed in over 40 serially sectioned rat fetuses of 10 to 21 days fetal age, from mothers fed a pteroylglutamic acid-deficient diet from the ninth to eleventh day of pregnancy. This period of deficiency produced the highest incidence (57 per cent) of cardiovascular abnormalities.

Some of the following abnormal processes were encountered: (1) the formation, regression or modification of aortic arch arteries is frequently disturbed during the eleventh to fifteenth days and results in abnormalities, such as double aortic arch, right aortic arch and absence of the ductus arteriosus; (2) the pulmonary arteries appear on the thirteenth day (twelfth day in controls) and may unite to form a single vessel which supplies both lungs; (3) regression of the right umbilical vein (thirteenth day in controls) may not occur and thus the right, instead of the left, umbilical vein persists until birth; in such cases there is no ductus venosus; (4) the cranial migration of the subclavian arteries along the descending aortas (fourteenth day in controls) may be delayed, predisposing to distal origin of a subclavian artery; (5) the truncus arteriosus may fail to divide (fourteenth day in controls) and thus persists in whole or in part; (6) closure of the interventricular foramen (about sixteenth day in controls) may be delayed or absent and is frequently associated with incomplete septation of the bulbus cordis, and (7) occasionally the left, instead of the right, umbilical artery persists beyond the seventeenth day.

**Myocardial Extraction of Oxygen, Glucose, Potassium and Inorganic Phosphorus in Dogs Cooled to 30 C. and Rapidly Rewarmed to 36 C.**

*A. Vernon Montgomery, Sylvan B. Baer and Henry Swan, Denver, Colo.*

Eleven dogs were anesthetized with chlorolose, cooled to 30 C. by immersion in ice water, maintained for 1 hour, rewarmed to 36 C. by immersion in water at 42 C. and followed for 3 more hours. The respiration was not assisted at any time. Coronary flow rates were determined at the above points along with arteriovenous differences across the myocardium of $O_2$, $CO_2$, $K^+$, glucose and inorganic phosphorus. Myocardial $O_2$ consumption decreased to about 50 per cent of control when cooled to 30 C. Upon rewarming, the myocardial $O_2$ consumption remained depressed. This was due to a failure of the coronary flow to return to control level, rather than to a change in arterio-venous $O_2$ difference. However, when the $O_2$ consumption is related to the left ventricular work, it is seen that instead of myocardial hypoxia, there is actually a loss of efficiency in the conversion of aerobic energy into mechanical work. When cooled, animals showed a marked positive $K^+$ and inorganic P myocardial balance. This positive balance is maintained upon rewarming. There is a linear relationship between the myocardial extraction of inorganic P and $K^+$. Glucose extraction by the myocardium is about 50 per cent of control when the dogs are cooled to 30 C, and remains depressed for at least 3 hours after rewarming.

**Prolonged Anticoagulant Therapy in the Management of Coronary Artery Disease**

*Edwin J. Morrow, Joseph T. Painter and Paul V. Ledbetter, Houston, Tex.*

One hundred and fifteen patients with proven coronary artery disease were maintained on prolonged anticoagulant therapy with Dicumarol as an adjunct to the routine treatment. Ages ranged from 26 to 82 years. The average duration of treatment was 2.5 years with overall figures varying from 1 month to 5 years. Treatment was continued following routine anticoagulation for myocardial infarction in 25 per cent of the cases, the remainder were started on Dicumarol for coronary insufficiency and impending infarction. Therapy was initiated in the hospital in all cases and was controlled by frequent visits and the utilization of Quick's bedside prothrombin time technic, which is discussed. Of the 115 cases, 20 per cent died while on therapy, 11.3 per cent of these or 13 cases, having had coronary occlusion in the past. The remaining 10 patients were under treatment for coronary artery disease without infarction, prior to sudden death. Hematuria occurred in 3 patients (2.6 per cent) while on therapy, as the only hemorrhagic manifestation. This complication was promptly controlled by discontinuing Dicumarol and by intravenous administration of vitamin $K_1$ oxide.

The principles and rationale of prolonged anticoagulant therapy as an adjunct to other accepted forms of treatment in this disease, as well as contraindications to its use, are discussed. Results are

ompared with those of other series to substantiate ur belief that routine careful long-term anti-oagulation with Dicumarol materially reduces the hances of occlusion of the coronary vessels and ffers a safe, effective and positive addition to ther forms of treatment.

**Mecamylamine in the Therapy of Hypertension**

*John H. Moyer, Edward Dennis, Ralph Ford and Coleman Caplovitz, Houston, Tex.*

When currently available, ganglionic blocking agents, used in the treatment of hypertension, produce a variable day to day reduction in blood pressure. This is due for the most part to incomplete and variable absorption of the drug from the intestinal tract. Mecamylamine, a secondary amine, is the first known autonomic blocking agent which is orally effective and is completely absorbed. The hemodynamic effects have been studied in the laboratory and in patients with hypertension. In dogs, mecamylamine produced the same cardiovascular and renal hemodynamic effects observed with such autonomic blocking agents as hexamethonium and pentolinium. When given to patients with hypertension, mecamylamine produced a consistent reduction in blood pressure which was most marked in the upright position. The effect was about equivalent when given orally or parenterally; the average daily dose was approximately 5 mg., twice a day. The onset of action ranged from one-half to 2 hours and the duration of action lasted 6 to 36 hours. The response was quite variable from patient to patient, but within the same patient it was reproducible, thus minimizing one of the chief objections to ganglionic blocking agents for the treatment of hypertension. Renal function was not altered unless the blood pressure was reduced excessively.

**An Experimental Study of Toxic Factors in Angiocardiography**

*J. Gerard Mudd, Julio C. Wong, John P. Wyatt and C. Rollins Hanlon, St. Louis, Mo.*

Due to an appreciable morbidity and a variable mortality associated with angiocardiography, an attempt to elucidate the cause of deaths during angiocardiography was studied in the mongrel dog. Urokon (sodium 3-acetyl-amino-2,4,6-triiodo benzoate) was injected into the anesthetized animal at the jugular vein, the main pulmonary artery (or right ventricular outflow tract) and the right or left pulmonary artery.

Seventy per cent Urokon was used in a dose of 1 cc. per Kg. of body weight in all cases. Arterial blood oxygen saturations were recorded and low saturations were obtained by inhalation of low oxygen gas mixtures. The lung was observed by direct visualization and sections were studied for microscopic changes both immediate and delayed.

There is a common reaction of agglutinative thrombosis in the pulmonary vasculature, particularly the alveolar capillaries which seems related to the hypertonicity of the injected contrast media. The severity of the reaction is related to the site of the injection and to some extent the degree of arterial unsaturation at the time of injection. With progression of the injection site from jugular vein to pulmonary artery, the reaction in the pulmonary parenchyma is progressively more severe. The reaction appears to be worse in those animals having low arterial oxygen saturation. The occurrence of edema, congestion and capillary permeability play a role in the delayed reaction of recovery and is commented upon briefly. The practical importance of these studies in contrast radiography of the vascular system is discussed.

**The Use of High Thoracic Leads for the Diagnosis of Infarction of the Base of the Left Ventricle**

*Gordon B. Myers and Frederick N. Talmers, Detroit, Mich.*

In many cases of autopsy-proven massive anterolateral infarction, all Wilson leads facing the epicardial aspect of the infarcted apex of the left ventricle (usually $V_4$ to $V_8$ inclusive) displayed initial slurred or notched R waves instead of diagnostic QS and QR complexes. The absence of Q waves from these leads may be correlated with infarction of the left side of the apical portion of the septum and consequent reversal of its activation to a right-to-left vector. The presence of infarction could often be established in such cases from the finding of abnormal QS and QR complexes in high thoracic leads $HV_3$ to $HV_8$ inclusive, taken at the intersections of a horizontal line at the level of the sternal and of the third interspace with the customary vertical lines. The presence of abnormal Q waves in high thoracic leads was correlated with infarction of the subjacent anterior, lateral or posterior aspect of the base of the left ventricle, together with sparing of the base of the septum and was attributed to undisturbed activation of the base of the septum in the usual left-to-right vector. The relatively rare infarcts confined to the anterior, lateral and posterior aspects of the base of the left ventricle could be recognized from high thoracic leads but not from the customary Wilson or limb leads. The abnormal QS and QR complexes in high precordial leads will be differentiated from the normal QS complexes associated with right ventricular dilatation and clockwise rotation of the heart and from the normal Q waves associated with uncomplicated left ventricular hypertrophy and incomplete left bundle branch block.

### The Hazard of Undue Delay in the Surgical Treatment of Traumatic (False) Aneurysms

*Robert A. Nabatoff, New York, N. Y.*

Traumatic aneurysms are not common in civilian life. A series of patients is described in which alarming, sudden hemorrhage occurred weeks after the initial injury. In view of the hazard of undue delay, traumatic aneurysms should be operated upon as soon as all infection and hematoma have subsided and the collateral circulation appears to be adequate. During the preoperative period it is essential to observe the patient closely in order to detect any sudden complications. The aneurysm should be excised and arterial continuity re-established, if this is feasible. If there is considerable infection or dead space, or if the wall of the involved vessel is so diseased that it cannot be sutured, ligation and division of the vessel immediately proximal and distal to the aneurysm should be carried out. Before obliterative procedures are performed, the collateral circulation must be tested and found to be adequate. Preoperative lumbar sympathectomy is a valuable adjunct in therapy since it minimizes vasospasm and allows for the maximum development of collateral circulation.

Four cases are described in detail, in order to illustrate the step-by-step preoperative, operative and postoperative management of these lesions. Each case represents a distinctly different type of surgical management and yet they have all had satisfactory long-term results. This emphasizes the fact that each patient must be considered an individual problem and that there is no one method of treatment for all cases of traumatic aneurysm. In all patients a good collateral circulation was achieved, even though arterial ligation was necessary in several instances.

### Ventricular Septal Defect with Pulmonary Stenosis: A Spectrum

*Alexander S. Nadas, Walter T. Goodale and John M. Craig, Boston, Mass.*

The purpose of this paper is to present the spectrum of the different clinical and physiologic entities resulting from the anatomic combination of ventricular septal defect and pulmonary stenosis.

All patients with ventricular septal defects and pulmonary stenosis show: (1) typical stenotic systolic murmur at the left sternal border; (2) x-ray evidence of right ventricular enlargement; (3) ECG proof of right ventricular hypertrophy or incomplete right bundle branch block without giant pulmonale. At cardiac catheterization, right ventricular hypertension with a gradient through the right ventricular outflow tract is demonstrated.

If, in a member of this large group of patients, the resistance at the infundibulum or rarely at the pulmonary valve, is greater than the systemic resistance, the characteristics of tetralogy of Fallot resulted. If the site of the dominant pulmonary resistance is at the arteriolar level with only a slight increase at the pulmonary valve, a variety of Eisenmenger's syndrome will be observed clinically. Finally, if the systemic resistance is higher than the total pulmonary resistance, the clinical picture of Roger's disease or pulmonary stenosis with a left to right shunt will be noted.

Although in most instances the relative size and site of the resistances is fixed in infancy, occasional transitions from one to the other group is demonstrable either momentarily during exercise or through horizontal follow up through the years.

A recognition of the fact that these widely varying clinical entities may have very similar underlying anatomic abnormalities helps in understanding the natural history of these patients and clarifies the existence of the intermediate stages between the well defined entities. It encourages, furthermore, the cardiologist and the surgeon to advocate shunt procedures for patients who are fully saturated at rest, but who develop severe atrial unsaturation on exercise. Examples of the individual entities, of the transitional stages and of the therapeutic results are presented.

### A Test of the Einthoven Triangle and a Modification which Corrects for the Lateral Eccentricity of the Heart

*C. V. Nelson and H. H. Hecht, Salt Lake City, Utah*

The trigonometric form of the Einthoven triangle with the heart in its center is expressed as

$$\tan \alpha_f = \frac{-(e_2 + e_3)}{\sqrt{3}\, e_1} \qquad (1)$$

where $\alpha_f$ is the angle between the projection of the heart vector on the frontal plane and the +x-axis. By assuming that the heart lies on a line from the center of the triangle to the left arm apex, it can be shown that

$$\tan (\alpha_f - 30^\circ) = \frac{2A' + B'}{\sqrt{3}\, B'} \frac{-e_2}{e_1 - e_3} \qquad (2)$$

where $A'$ = distance from right side to center of excitation, and $B'$ = distance from left side to center of excitation. $A'$ and $B'$ can be estimated from an x-ray photograph of the subject. At the center of the triangle, the two equations give the same value of $\alpha_f$.

The equations were checked in an electrolytic tank model of the human thorax, employing an artificial dipole. To test (1), the dipole was located in the sagittal plane but was eccentrically displaced towards the front and top of the tank. To test (2), the dipole was shifted towards the left side as well.

If $\alpha$ (in contrast to $\alpha_f$) is defined as the angle between the heart vector and the horizontal *plane*, and $\beta$ as the angle between the projection of the vector on the horizontal plane and the +x-axis, then

$$\tan \alpha_f = \frac{\tan \alpha}{\cos \beta} \qquad (3)$$

For values of $\alpha = 0°, 30°, 60°$ and $90°$, $\alpha_f$ was determined as a function of $\beta$. $\alpha_f$ was also calculated from either (1) or (2).

For $\alpha = 30°$, the experimental values of $\alpha_f$ vary between the limits 30° and 150° as $\beta$ goes through a complete revolution. For $\alpha = 60°$, $\alpha_f$ varies between 60° and 120°; for $\alpha = 90°, \alpha_f = 90°$ and for $\alpha = 0°$, $\alpha_f = 0°$ or 180°. The calculated values agreed fairly well with those measured, being generally lower than the experimental values. With the heart in the center of the triangle, the error was larger than when eccentrically placed. The experiments show that the Einthoven triangle method does give the value of $\alpha_f$ approximately and that the modified equation (2) holds for lateral displacements. One must also know $\beta$, however, in order to determine $\alpha$, the true angle of the vector with the horizontal plane.

### The Study of the Prodromal Syndrome of Myocardial Infarction

*Walter Newman, New York, N. Y.*

We have studied a series of 31 patients with the prodromal syndrome of myocardial infarction in an attempt to elucidate its natural history and the value of anticoagulants.

The duration of the syndrome was less than one week in 12 per cent of the cases, 1 to 4 weeks in 30 per cent, 4 to 12 weeks in 36 per cent and 12 weeks to 9 months in 22 per cent. Attacks occurred as frequently as every 2 hours and as seldom as 3 times in 3 months. Approximately one-half of our cases went on to develop a typical anginal syndrome, one-fourth became asymptomatic, one-fifth developed myocardial infarctions and 2 patients, when last seen, were still in the prodromal stage.

All 31 of our cases were treated with bedrest. Seventeen cases received anticoagulants on a randomized basis for periods lasting from 3 to 9 weeks. None of our patients developed a myocardial infarction while on anticoagulant therapy whereas 9 patients (in the entire series) did develop a myocardial infarction while not receiving anticoagulants. Four patients who received anticoagulant therapy for the prodromal syndrome continued to have chest pain. Three of these patients were taken off anticoagulants and developed a myocardial infarction within 4, 10 days and 21 days, following cessation of therapy. Six patients on anticoagulants developed the anginal syndrome and 2 of these sustained myocardial infarctions at a later date when anticoagulants had been stopped. Finally, 7 of the patients who had received anticoagulants were returned to an asymptomatic state and have remained asymptomatic at their most recent follow-up despite cessation of their anticoagulant therapy.

On the other hand, of the patients, who did not receive anticoagulants, none are asymptomatic, 10 were left with the anginal syndrome, 3 developed a myocardial infarction and 1 still manifests the prodromal syndrome.

### The Genesis and Clinical Implication of the Sharp First Sound in Mitral Stenosis

*Henry T. Nichols, William Likoff and Philip Lisan, Philadelphia, Pa.*

This investigation correlates the pathology and mechanical function of the deformed valves with the laws of acoustics in an effort to define the genesis and implication of the short, high-pitched, or "sharp" first sound. This study is based on observations of normal and stenotic mitral valves during cardiac surgery, and on simultaneous recordings of sounds and ventricular pressures at operation.

When the leaflets of the stenotic valve retain some flexibility, the gentle bulging of the cusps into the atrium with ventricular systole, which is seen in the normal valve, becomes abrupt as if the buffering action of the supporting structures has been lost. This movement always is associated with a "sharp" sound.

Acoustically, such a valve is a two-dimensional stretched membrane, the vibrations of which result in a short high-pitched sound only when the tissue inertia and tension are increased, and the length and mass are decreased. The rheumatic fibroblastic proliferation produces these specific conditions. Since the leaflets are relatively immobile, the abrupt intra-atrial bulging also is delayed, and the sound occurs late in the isometric period.

If the leaflets are rigid with calcification, intra-atrial bulging does not take place and a "sharp" sound is not heard. This valve functions as an acoustic diaphragm, the vibrations of which are low-pitched because the decreased tissue elasticity is the sole determinant independent of tension, length, or mass. Since abrupt leaflet bulging does not take place, the first sound is not delayed.

Although stenosis reduces the contacting force of mitral leaflets, this does not decrease the likelihood of the "sharp" sound. Clinically, when a "sharp" first sound is heard in mitral stenosis, it implies retained leaflet flexibility. However, since the sound is not produced by far advanced stenosis with rigid cusps, its absence does not negate the basic diagnosis.

### A Study of Changes in Serum Concentrations of the Enzyme, Glutamic Oxalacetic Transaminase, in Rheumatic Fever

*Irwin Nydick, James Tang, Gene H. Stollerman, Felix Wróblewski and John S. LaDue, New York, N. Y.*

A simple, accurate, spectrophotometric test for the analysis of the serum concentration of the enzyme, glutamic oxalacetic transaminase (SGO-T) has been previously devised. Studies have shown this enzyme to be most concentrated in heart muscle and to rise precipitously in the serum following myocardial necrosis in man and experimental animals. The theoretic and clinical importance of testing for necrosis of the myocardial fibre, per se, in rheumatic fever is the basis of the present study.

Sixty-four rheumatic subjects in all stages of the disease were studied. Of 26 patients with clinically active carditis, 17 had significant elevation of SGO-T activity at some time during this stage. Of 18 "inactive" patients with a definite recent or past history of carditis, all serums analyzed were within the range of normal. Twelve patients with non-cardiac rheumatic manifestations were studied, only 1 developed abnormal serum concentrations of SGO-T. This patient subsequently developed equivocal signs of an active carditis. Eight rheumatic subjects who developed virus pneumonia were studied. In one, an evanescent, slight elevation of SGO-T was seen at a time when his ECG showed grossly abnormal T waves, probably the result of mild myocarditis, occasionally seen with virus pneumonia.

There was no obvious relationship of the SGO-T levels to the various "acute phase reactants." The erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and white blood count (WBC) were normal during antirheumatic therapy, there were often striking rises of SGO-T.

The clinical course of carditis did not consistently parallel fluctuations in the enzyme levels. Some patients with severe carditis and congestive heart failure had normal levels, others with low-grade carditis were seen with 5-fold increases.

Microscopic study of atrial appendages (operative specimens) was done in 12 patients and tissue obtained at autopsy was available in 3 patients. The SGO-T was abnormal at some time in 5 of 10 patients with at least one of the following microscopic signs of inflammation: Aschoff's nodules, round cell infiltrations, acute myocardial necrosis, fibrinoid degeneration of collagen. Of the 5 patients with no microscopic evidence of inflammation, only 1 showed an elevation of the SGO-T. Extensive fibrous replacement of myocardial fibres was seen at autopsy in this patient. Aspirin and steroid therapy have had variable relationships to changes in the SGO-T in the few patients studied.

### Pseudo-Ventricular Arrhythmias in Wolff-Parkinson-White Syndrome

*J. Roscoe Oates, George R. Herrmann, Tom M. Runge and M. R. Hejtmancik, Galveston, Tex.*

We have observed very startling ECG patterns during rapid heart action in 6 patients who later proved to have Wolff-Parkinson-White Syndrome (WPW). It is the purpose of this paper to describe our experiences.

Most episodes of rapid heart action in WPW are, by ECG study, definitely atrial in origin, being either atrial tachycardia or fibrillation. But on occasion, ECGs, which appear to show ventricular tachycardia or even ventricular fibrillation, are encountered. The WPW literature now contains a fair number of papers which describe ventricular arrhythmias in WPW patients. Careful analysis has shown that our six cases of this type represented atrial arrhythmias which ECG-mimicked ventricular arrhythmias.

Of the cases which showed pseudo-ventricular tachycardias, none showed P waves, occurring at a rate different from that of the ventricular complexes. This, of course, is essential for the absolute diagnosis of ventricular tachycardia. Most of the ECGs, in fact, showed P waves occurring at the same place within each ventricular complex. Of the cases which showed pseudo-ventricular fibrillation, none showed syncope, shock or any signs of imminent danger of death clinically; and all recovered after medical treatment alone.

All of the cases responded to intravenous procaine amide (Pronestyl) by reverting to typical ECG patterns of WPW and to normal cardiac rates; these complexes were, of course, sino-atrial in origin. Comparison with the pseudo-ventricular ECGs taken before treatment showed that, save for changes attributable to differences in rate, the QRS complexes before and after treatment were entirely comparable, lead-by-lead.

The genesis of these bizarre ECGs is unknown. Whatever their mechanism, we feel that true ventricular arrhythmias almost never occur in WPW. The presence of very rapid heart action (260 per minute or more), regular or irregular, is diagnostic of accelerated WPW conduction of an atrial mechanism disorder.

### A Reappraisal of the Cardiac Physiopathology in Patients with Interventricular Septal Defect

*James E. Odell, L. E. January, John W. Eckstein and James W. Culbertson, Iowa City, Ia.*

The customary statement is that patients, exhibiting interventricular septal defect as the sole cardiac lesion, show evidence of left ventricular hypertrophy by ECG study, fluoroscopy and necrospy. This has led to the assumption that the

left ventricle bears the major burden of generating the excessive pulmonary blood flow and also to the implication that most of the shunted blood traverses the interventricular septum during ventricular systole.

Data were analyzed from 15 patients, proven by cardiac catheterization to have interventricular septal defect alone. This was diagnosed only when right ventricular blood oxygen content exceeded average right atrial level by at least 1.0 ml. per 100 ml. Physical and fluoroscopic examinations indicated right ventricular enlargement rather than left in all patients. Electrocardiography provided evidence of purely right ventricular abnormality in 12 of 15 patients. Three standard, three augmented unipolar limbs, and nine unipolar precordial leads $V_{4R}$-$V_7$ were recorded and interpreted according to the criteria of Myers. Crucial evidence often was obtainable only in leads $V_{3R}$ and $V_{4R}$.

The finding of primary enlargement and hypertrophy of the right ventricle implies that the major portion of the arteriovenous shunting occurs during ventricular diastole and that the development of left ventricular hypertrophy occurs in some patients as a late complication. The evidence for solitary right ventricular involvement in most patients of this series refutes commonly accepted clinical criteria for diagnosis of interventricular septal defect and demonstrates how this lesion can be confused with interatrial septal defect and with pulmonic stenosis, the differentiation of which is highly important in deciding surgical therapy. This study emphasizes the importance of routine recording of leads $V_{3R}$ and $V_{4R}$ in patients with congenital heart disease. Subsequent experience suggests the usefulness of $HV_1$ and $HV_2$ as well.

**Effect of Acetyl Strophanthidin upon the Myocardial Metabolism and Cardiac Work of Normal Dogs and Dogs with Congestive Heart Failure**

*Robert E. Olson, George Roush and Maria M. L. Liang, Pittsburgh, Pa.*

Chronic congestive heart failure, characterized by edema, ascites, weakness, reduced exercise tolerance, cardio- and hepatomegaly and elevation of end-diastolic right ventricular filling pressures, has been produced in dogs by surgical avulsion of the tricuspid valve and stenosis of the pulmonary artery. Animals in congestive heart failure and normal controls were then digitalized with the rapidly acting acetyl strophanthidin under mild barbiturate-morphine-urethane anesthesia and the changes in cardiac metabolism and cardiac work observed over a period of 4 hours.

In order to obtain pre-treatment arterial levels of glucose which would produce a reasonable myocardial extraction rate for this substrate, intraperitoneal glucose was administered throughout the experiment. Acetyl strophanthidin was administered at the rate of 0.2 mg. per 3 minutes until runs of ventricular tachycardia were evident. The dose required to produce this endpoint was about 0.1 mg. per Kg. in the normal dogs and about 0.03 mg. per Kg. in those with failure. Measurements of cardiac output, arterial and venous pulse tracings, myocardial oxygen consumption, carbon dioxide production and myocardial extraction of glucose, pyruvate and lactate were made at the height of the action of the drug and at 2 hours and 4 hours thereafter. Acetyl strophanthidin had a slightly negative inotropic effect in the normal dog and a positive one in the dog with congestive heart failure. The most conspicuous effect of the drug upon myocardial metabolism was a reduction in glucose uptake, without an appreciable effect upon the extraction of oxygen, pyruvate or lactate.

The effects are consistent with a two-fold action of strophanthidin upon cardiac metabolism, i.e. an inhibitory effect upon glucose metabolism and a variable effect upon the contractile proteins, depending upon their state of competence. A relationship may exist between the contractility of cardiac muscle and certain physical-chemical properties of myosin which may serve as a basis for the variable effect of strophanthidin in the normal and failing heart.

**The Effect of Tilting on the Right Atrial Pressure of Patients with Heart Failure**

*B. M. Oser, J. R. Huston and J. M. Ryan, Columbus, O.*

The effect of upright tilting on right atrial pressure was determined in 24 patients with heart disease of various types. Seven had no failure, the rest had moderate to advanced failure with anasarca. Ten controls included 7 normals and 3 with massive non-cardiac edema.

Supine, a point half the distance from the front to the back of the chest, at the fourth right intercostal space, was our reference. Upright, the catheter tip in the mid-right atrium (fluoroscopically) was the reference. Pressures were determined in mm. $H_2O$ with a water manometer.

Subjects, with and without heart disease and also with and without edema, having a recumbent pressure of 100 or less, had an average pressure drop of 81 when upright. Those with recumbent pressures between 100 and 200 had an average drop of 94 while those with recumbent pressures greater than 200 had an average drop of 166 when tilted. A direct correlation of 0.65 exists between the recumbent pressure and the total fall of this pressure after tilting ($p < 0.01$).

It appears that in advanced congestive failure the vascular bed remains distensible. When upright, the increased venous hydrostatic pressure below the diaphragm may exceed venous tone and

result in blood trapping, thus reducing right atrial pressure. The effect is probably similar on pulmonary venous pressure. Since elevated pulmonary venous pressure may be a respiratory stimulus, an orthostatic reduction in this pressure would help explain orthopnea and also the relief of paroxysmal nocturnal dyspnea. A venous pressure-volume diagram shows that the higher pressures occupy the flat slope of the curve where volume changes cause the greatest pressure changes. The orthostatic decrease in intrathoracic pressure probably accounts for only a small portion of the atrial pressure change.

**Serum Transaminase: A Clinical and Electrocardiographic Correlation in Patients with Suspected Myocardial Infarction**

*Bernard H. Ostrow, Daniel Steinberg, Howard E. Ticktin and John M. Evans, Washington, D. C.*

This study was designed to evaluate serum glutamic oxalacetic transaminase (SGO-T) in patients, hospitalized within 96 hours from onset of chest pain which were suspected to be of coronary origin. Serial ECGs, serum transaminase, erythrocyte sedimentation rate, and white blood count tests were done. The ECG findings were classified into 5 groups: group 1, acute transmural myocardial infarction with Q waves diagnostic of necrosis; group 2, normal; group 3, left ventricular hypertrophy and strain, myocardial ischemia and digitalis effect; group 4, subendocardial ischemia and group 5, masking ECGs, such as bundle branch block, Wolfe-Parkinson-White syndrome, pericarditis and previous infarction.

There were 102 cases in the series, 43 were in group 1 and all had elevated SGO-T. The average peak, 164 units per ml., was reached from 2 to 96 hours after onset of pain (average at 27 hours). The average peak erythocyte sedimentation rate and white blood count was 35 mm. per hour and 14,400 per cu. mm., respectively. Body temperature reached a height of 38 C.

There were 59 cases, suspected by ECG study of myocardial infarction without transmural infarction. The clinical course and the ECG findings were compared with those cases having group 1 ECGs without prior knowledge of the SGO-T values. Nine patients in group 2, were considered clinically negative for infarction and 7 had normal SGO-T levels. There were 30 subjects in group 3, 8 were clinically positive for infarction, 6 had elevated SGO-T levels; 22 were negative clinically and 18 had normal SGO-T levels. There were 3 in group 4, 2 clinically positive, both with elevated SGO-T values and one with a negative clinical course and normal SGO-T. There were 16 cases in group 5, 8 negative clinically, all with normal SGO-T and 8 positive clinically, of these, 6 had elevated SGO-T. It would appear that serum glutamic oxalacetic transaminase levels are of value in confirming acute myocardial infarction, when the clinical course and ECG findings are inconclusive.

**The Electrocardiograms of Patients with Atrial Septal Defects before and after Surgical Repair**

*Thomas W. Parkin and Howard B. Burchell, Rochester, Minn.*

The ECGs of 41 patients with atrial septal defects before and after surgical repair have been studied. The majority of postoperative ECG studies were made during the first month after operation, although the period ranged from 1 day to 1 year. Such variables as the patient's age, systemic and pulmonary arterial blood pressures, cardiac size and medication with digitalis and the like were assessed. All patients underwent cardiac catheterization before operation and the majority, also after operation. Such data were correlated with ECG patterns and the latter were placed into 2 general categories: those indicating increased right ventricular work load and those not indicating it.

Before operation, 2 patients had atrial fibrillation and one had atrial flutter. Increases in the amplitude (more than 0.2 mv.) and duration (0.1 second) of the P waves in leads II and III were common. Twenty-six patients had a pattern of incomplete right bundle-branch block and 9 had complete right bundle-branch block (QRS more than 0.12 second).

After operation, the size of the P waves decreased in leads II and III. Supraventricular tachycardia occurred in 3 patients, and atrial flutter or fibrillation or both occurred in 11. Arrhythmia developed from 1 day to 2 months after operation and lasted from several hours to 8 months. Either no changes or minimal ones were noted in the QRS complexes. Elevation or depression of the S-T segments and inversion of T waves developed frequently in the early postoperative period. These changes were attributed to operative manipulation of the heart and pericardium.

Two patients were found to have persistent common atrioventricular canals or partial forms thereof which, before operation, simulated atrial septal defects hemodynamically. These ECG studies were not distinctive from those of patients with common types of atrial septal defect.

**A Review of One Hundred Successful Kidney Biopsies**

*Alvin E. Parrish and John S. Howe, Washington, D. C.*

In evaluating a new procedure, such as needle biopsy of the kidney, it is important to know the ease of performance, resulting morbidity and

mortality and its clinical usefulness. The first 2 points have been fairly well covered previously by the authors and by others. In order to assess the clinical usefulness, 100 successful renal biopsies were reviewed and compared with the clinical impressions. These were taken from a total of 169 biopsy attempts of which 131 yielded renal tissue. However, the results in 31 biopsies, were discarded because they were either unsatisfactory or were repeat biopsies on the same patients.

Kidney biopsies were obtained by means of a Turkel needle, and were considered adequate only if at least 10 glomeruli were present. Clinical diagnoses were made by carefully evaluating the history, physical examination and laboratory data.

Renal biopsy established the diagnosis in 52 per cent of the patients; it confirmed the clinical impression in 39 per cent of the cases and in 9 per cent, neither the pathologist nor the clinician could make a definite diagnosis. Renal biopsy was of least help in acute glomerulonephritis and acute pyelonephritis. It was of considerable value in the diagnosis of intercapillary glomerulosclerosis, chronic glomerulonephritis, nephrosclerosis, and rare diseases of the kidney, such as polycystic disease, amyloidosis, and metastatic carcinoma.

**Dynamics of Acute Failure of the Left Ventricle during Neurogenic Hypertension**

*J. L. Patterson, Jr. and H. G. Langford, Richmond, Va.*

The circulatory dynamics associated with the acutely failing left ventricle were investigated by the induction of acute myocardial necrosis and sudden hypertension. Repeated injections of zinc hydroxide were made transcutaneously into the left ventricular myocardium in fourteen dogs. This produced necrosis of 15 to 50 per cent of the left ventricular myocardium and hypertension was induced by electrical stimulation of the cerebral motor cortex for 60 to 180 seconds. Pressures were measured with strain gages before and after dextran infusion and cardiac output, by dye dilution. Thirteen control animals were similarly studied.

With cortical stimulation, mean aortic pressure rose by 63 mm. Hg in the experimental animals, compared with 86 mm. Hg in the controls. This was due to systemic vasoconstriction since cardiac output fell slightly. Calculated cardiac work increased 22 per cent in the experimental animals, 36 per cent in the controls. Pulmonary arterial and capillary (wedge) pressures showed small rises in the experimental and control animals during stimulation.

After infusion of 20 to 30 ml. dextran per Kg., stimulation produced increases in mean aortic pressures of 60 and 64, with resulting mean values of 203 and 221 mm. Hg in experimental and control dogs. Plasma volume expansion alone caused marked increase in cardiac output in both groups. However, cortical stimulation and further rise in arterial pressure caused a 22 per cent fall in cardiac output in the experimental animals, but no change in the controls. Dextran infusion resulted in slight wedge pressure rise in controls, with little further change during stimulation. In the experimental dogs, infusion alone produced an 11 mm. Hg rise in capillary pressure. An additional 10 mm. mean increase on stimulation resulted in pressures over 35 mm. Hg and gross pulmonary edema in five animals.

These observations show that a severely injured left ventricle can support acute hypertension and large increases in cardiac work for brief periods but at the price of high filling pressure. Increase in blood volume can play a critical role in acute left ventricular failure by: (1) producing excessive increase in left ventricular filling pressure beyond the optimal; (2) causing large increases in cardiac work and (3) apparently acting as an essential factor in the production of extreme levels of pulmonary venous pressure.

**Experimental Induction and Termination of Cardiac Arrhythmias by Externally Applied Electric Current**

*Milton H. Paul, Paul M. Zoll, Leona R. Norman, Arthur J. Linenthal and William Gibson, Boston, Mass.*

By the external application of 2 forms of electric current, it has been possible, in animals, to control the cardiac rhythm, to induce many of the clinically significant cardiac arrhythmias and to terminate these arrhythmias instantaneously.

Monophasic impulses of 3 msec. duration, applied across small electrodes on the intact chest in dogs and pigs, stimulated effective cardiac beats of atrial or ventricular origin and produced intermittent or multiple ectopic beats or replaced the intrinsic rhythm completely.

At high rates of stimulation, above 500 per minute, cardiac responses became irregular but cessation of stimulation was usually followed by the return of normal sinus rhythm. After preliminary ligation of the terminal left circumflex coronary artery in 12 pigs, stimulation at rapid rates frequently induced significant arrhythmias. Arrhythmias were produced regularly over a period extending to at least 4 weeks, following coronary ligation. Atrial fibrillation was induced 13 times, supraventricular tachycardia 6 times and ventricular tachycardia 37 times; ventricular fibrillation followed rapid stimulation in 23 instances.

A second form of electric current, i.e. countershock with 60 cycle alternating current (180 to 300 v., 0.1 second duration), was applied externally to these animals across the closed chest with large electrodes (15 by 15 cm.) and was effective in

terminating all forms of cardiac arrhythmia instantaneously. Atrial, nodal and ventricular tachycardias as well as atrial and ventricular fibrillation were regularly terminated and converted to normal sinus rhythm in most instances. The efficacy of externally applied current in terminating cardiac arrhythmias was clearly established by the *repeated* observation of the *immediate* cessation of the irregularity after countershock.

Externally applied monophasic impulses have served as an artificial cardiac pacemaker to resuscitate patients from cardiac arrest. External countershock, with alternating current, may prove similarly useful in man for the immediate termination of tachycardia or fibrillation.

**Cardiac Metabolism in Myocardial Ischemia**

*A. Pedersen, A. Siegel, W. S. Edwards and R. J. Bing, Birmingham, Ala.*

The cardiac metabolism of glucose, pyruvate, lactate, amino acids, ketones, fatty acids and electrolytes was studied using coronary sinus intubation in a series of 90 anesthetized closed-chest dogs. Myocardial ischemia was produced by hemorrhage, embolization of the coronary arteries with plastic spheres and ventricular fibrillation. In all 3 conditions, pyruvate appeared in increased concentrations in coronary vein blood. In hemorrhagic shock, myocardial utilization of lactate was increased; in contrast, embolization of the coronary arteries and ventricular fibrillation resulted in many instances in negative myocardial glucose and lactate balances. In some experiments, concentrations of lactate in coronary vein blood exceeded those in arterial blood by more than 50 mg. per cent. The onset of ventricular fibrillation was followed by severe disturbances in myocardial extraction of amino acids, ketones, Na and K. The metabolic changes following coronary occlusion lasted only for a few minutes, despite persistent systemic hypotension. Moderate hypothermia (32 C.) had no influence on the metabolic changes induced by embolization of the coronary arteries. Severe hypothermia (25 C.) did not affect the changes in myocardial pyruvate and lactate extration but prevented the occurrence of negative myocardial glucose balance. The results demonstrated that myocardial ischemia produced by embolization of the coronary arteries and by ventricular fibrillation resulted in severe disturbances in the energy production within the heart muscle. Apparently, the rapidity, with which myocardial ischemia developed, influenced the severity of the metabolic changes. Occlusion of the coronary arteries results in the immediate passage of substances of small molecular weight into the coronary vein blood. Later, as necrosis of heart muscle develops, compounds of higher molecular weight (proteins, enzymes) enter the coronary venous system of the heart.

**A Thermoregulated Cool Box: A Substitute for a Thermoregulated Cool Room for Measuring Blood Flow in Peripheral Arterial Disease**

*Raymond Penneys, Philadelphia, Pa.*

In patients with peripheral arterial disease, the prime factor influencing the survival of the limb is the capacity for blood flow in the affected extremity. This can be measured by the reflex vasodilatation test, comparing digital skin temperature with the temperature of the surrounding air after all vasomotor tone in the limb is removed. The environmental air must be cool (approximately 20 C.) and reasonably constant (±1 C.), in order that the skin temperature to air temperature relationship be a valid measurement of blood flow. In the past, this exposure to cool air has required that the patient be placed in a thermoregulated cool room.

For the sake of economy, a simply constructed thermoregulated cool box has been substituted for the room. Only the distal portion of the extremity on which blood flow measurements are to be made is inserted in the box, the subject stays in an ordinary room. With this cool box, reflex vasodilatation tests were made on the feet of patients having peripheral arterial disease (31 observations) and of normal subjects (22) and the results were compared to those obtained by the standard test, using the cool room. Excellent agreement was found to exist between the 2 methods; the correlation coefficient (r) was 0.9 for the patients with arterial disease.

It appears, therefore, that a thermoregulated cool box may be used instead of a thermoregulated cool room in carrying out the reflex vasodilatation test. This should make reliable measurements of blood flow in the extremities more easily available in the daily management of peripheral arterial disease.

**Comparison of the Concentration of Several Trace Metals in the Urine of Treated and Untreated Malignant Hypertensive Patients as Compared with Normal Individuals**

*H. Mitchell Perry, Jr. and Henry A. Schroeder, St. Louis, Mo.*

Two hundred ml. of urine was collected from 14 patients with malignant hypertension. Precautions were taken to prevent contamination by any exogenous metal. These samples were treated to remove organic matter and were highly concentrated with 8-hydroxyquinoline. Titanium, vanadium, chromium, manganese, nickel, zinc, molybdenum, silver, cadmium, tin and lead were then measured by a quantitative spectrographic procedure, each sample being

lone in duplicate. The error determined by multiple runs on the same sample rarely exceeded 5 per cent. For 5 patients, similar determinations were made after treatment, from 7 to 20 days with hydralazine, which binds many of the metals in question. The urine of 6 normal individuals was similarly studied. The most significant differences were in manganese and cadmium. The 14 patients with malignant hypertension had an average of 40 parts per billion of cadmium, whereas normal patients had less than 1. Five hypertensive patients had 75 parts of cadmium per billion in their urine before treatment and less than 1 after treatment. An average of 60 parts of manganese per billion were found in the urine of the 14 hypertensive patients as compared with 12 parts per billion in the normal individuals. The change with hydralazine therapy in 5 patients was from a mean of 82 to 16 parts per billion. The entire group of hypertensives excreted an average of 8 times as much lead as did normal persons Before treatment 5 hypertensive patients only excreted twice as much, hence their achievement of the normal mean after therapy was less significant. The differences for the other metals were of lesser magnitude. Hydralazine apparently alters the abnormal excretion of some "essential" and exogenous trace metals in the direction of normal.

**Evidence for Reversal of the Hypertensive Process When Blood Pressure is Controlled by Drugs**

*H. Mitchell Perry, Jr. and Henry A. Schroeder, St. Louis, Mo.*

One hundred and fourteen hospitalized patients were treated only with oral hexamethonium chloride and hydralazine, in doses fluctuating according to their blood pressure. They were followed-up at home for at least 1 year, blood pressure and dosage records being made at 4-hour intervals. They were grouped on the basis of their mean pretreatment diastolic pressure, which was the average of more than 2,000 readings taken in the hospital. Forty patients had diastolic pressures between 100 and 115 mm. Hg, 41 from 115 to 130, and 33, from 130 to 180. Of the latter group, 58 per cent had hemorrhagic and exudative retinitis, 67 per cent had albuminuria and 30 per cent had azotemia. A month after discharge, the mean oral daily intake of hexamethonium chloride was 2.11 Gm. and of hydralazine 0.52 gms. A year after discharge, the mean diastolic pressure of 79 patients was less than 100 mm. Hg; 35 had not achieved this degree of control. The average hexamethonium requirement of the controlled group was 73 per cent of their initial dose, whereas the second group took an average of 97 per cent of their initial dose. Of 78 patients followed-up for 2 years, the 60, who had average diastolic pressures below 100 mm. Hg, required only an average of 57 per cent of their initial dose. The 18 patients, who had not achieved this control, continued to take 99 per cent of their hexamethonium chloride. The 37, followed for 3 years, required 41 per cent. No definite reduction in hydralazine intake was obvious at 1 year, but at 2 years the controlled group took 71 per cent and the uncontrolled group 86 per cent of their initial dosages. In from 12 to 42 months, 19 normotensive patients were able to discontinue hexamethonium without a return of high blood pressure. In 10, hydralazine was also discontinued without loss of control. These patients (4 had severe hypertension) showed a regression of secondary abnormalities as measured by renal function, ECGs and ocular fundi. Patients taking other drugs (reserpine, pentolinium) were excluded from this series.

**The Effect of Two Metal-Binding Agents on Plasma Cholesterol in Man**

*H. Mitchell Perry, Jr. and Henry A. Schroeder, St. Louis, Mo.*

Twenty patients were given from 3 to 27 Gm. of calcium ethylenediamine tetraacetate (EDTA) intravenously. After an average total dose of 17 Gm. and without change in other metal binding drugs the total plasma cholesterol temporarily fell to an average of 73 mg. per ml. of plasma. In all but 2, the nadir was between 120 and 150 mg. per cent. In two, initially low values failed to drop. This was compared with an average fall of 29 mg. following oral hydralazine therapy in 112 unselected hypertensive patients; those with high initial values (211 to 371 mg.) had a fall of 48 mg. per 100 ml. for 2 to 3 years. Patients with hydralazine toxicity were excluded from the series.

In 10 hypertensive patients who received an average of 15 Gm. of EDTA the blood pressure fell an equivocal 10 to 8 mm. Hg; 6 who took blocking agents required only 33 per cent of their control dose. A similar but sometimes less marked effect on cholesterol, appearing in 2 to 4 weeks, was observed in 7 of 9 patients, given the material orally. Symptomatic improvement was claimed by all 7 persons suffering from ischemic manifestations; objective changes were seen in only 1. The degree of change was greater than we have seen reported from other regimens. Lesions resembling B complex deficiency (riboflavin or $B_6$) appeared in two given large repeated intravenous doses. The mechanism of these changes is obscure but may be related to the removal of certain trace metals.

**Some Determinants of Total Peripheral Resistance**

*Lysle H. Peterson, Philadelphia, Pa.*

The factors within the vascular system which tend to resist the flow of blood which the heart

produces are (1) the mass being accelerated during systole; (2) the "rigidity" of the vessel walls during systole and (3) the resistance due to viscosity. The magnitude of these factors at any instant is manifested as blood pressure. The great complexity of the relationships of their magnitude to blood pressure is chiefly due to the complex distributed geometry of the vascular system. Factors (1) and (2) are usually not considered as resistance because there are no significant associated energy losses, since the mass being accelerated during systole gains kinetic energy and, together with the elastic energy stored in the stretched vessel walls, is recoverable during diastole. While they do not affect the overall energetics, when averaged over the cardiac cycle, they are, however, forms of considerable resistance to the contracting heart. The classical consideration of "peripheral" resistance is that given to viscosity. Its total magnitude is frequently measured by the ratio

$$\frac{\text{M. arterial pressure} - \text{M. central venous pressure}}{\text{mean (M.) cardiac output}}.$$

Just what is happening in a particular vascular system at a particular time when that ratio changes can only be largely speculation, at present. If it is implied that the ratio represents mechanical energy loss due to viscous friction, then it is assumed that no energy is added within the system (e.g., skeletal and respiratory pump) and that all energy loss appears as pressure drop.

If it is implied that changes in the ratio are due only to changes in the radius of blood vessels, then the implicit assumptions are that the vascular system can be considered to behave like a single, straight and rigid tube and that the effective viscosity of blood remains constant throughout the system. If it is implied that the chief site of vessel caliber change is the arteriole, then it is assumed that resistances and their ratios in other sites is comparatively small. Studies utilizing a black box forcing method have shown that (1) from 5 to 50 per cent of the mechanical energy provided by the heart may be lost within the distensible part of the arterial system, i.e., proximal to the arterioles; (2) the distensibility of the arterial system has been found to vary fourfold in the intact, living animal when epinephrine, norepinephrine or acetylcholine is introduced or when bleeding occurs; (3) the effective mass which must be accelerated during systole is also estimated to vary fourfold or more under similar influences.

**Present Status of Coronary Disease and Workmen's Compensation**

*Milton Plotz, New York, N. Y.*

Cardiac cases now represent an increasing percentage of the total number of cases coming before Workmen's Compensation Boards. Of these, claims involving coronary disease are the most frequent and most controversial. This is a source of concern to the general public and to the cardiologist as well; the latter, exercising both skill and good faith, may be hard put when asked to testify in such situations.

In an effort to assist the physician, the history of policy regarding coronary disease is reviewed and brought up to date. The development of Workmen's Compensation Laws from the original German legislation as modified by the English Common Law, is briefly traced. American practice with heart cases has undergone continuous evolution and modification. Since 1953, there has been a considerable degree of uniformity in the practice among the several states.

The present status of: (1) "usual versus unusual," (2) "accidental," (3) "previous disease" and (4) "continuing usual work after attack" is reviewed; most of the modifications assist the physician in his preparation of the case and his testimony. Generally speaking, the base for allowing compensation has been considerably broadened. In most states, the "unusual" nature of a preceding exertion is no longer stressed. The word "accidental" has come to mean "unexpected." "Previous heart disease" may now be conceded without fear of compromising a patient's claim. This widening of the sphere of allowable claims may result in unjust claims being advanced and may be a source of irritation to the physician but in some ways his task is made easier. The attitudes of New York and New Jersey do not quite agree with those of other states and this is discussed in detail.

**Clinical Use of Human and Prosthetic Grafts in Arterial Disease**

*Gerald H. Pratt, New York, N. Y.*

The place of autogenous grafts as replacements for injured or diseased arteries has been established. The difficulty of their acquisition, sterilization and storage has relegated this type of surgery to the few vascular clinics in metropolitan areas.

A prosthetic which would be universally available is the goal of most surgeons in this field. Solid containers or tubes have been ineffective. Various synthetics and particularly those made of the newer fabrics have had extensive trial in the laboratory animals.

The author has made implantation grafts, using a special nylon tube in 8 human patients. Immediate results have been exceptionally good. The technical ease with which these can be inserted has been impressive. Their fate over a long follow-up is not yet established. Their use however in the emergency presented by the acute occlusion is advocated, especially where an analogous graft would not be effective and a homologous graft is not available.

The work with these nylon tubes is compared with

he work done in this clinic with end-to-side vein grafts and end-to-end homologous grafts. The author's experience indicates that surgical sympathectomy is an important complement to this operation. Anticoagulant therapy has been utilized in all of this vascular surgery.

**Diastolic Murmurs of the Tricuspid Valve; Hypervolemic Murmurs in Patients with Atrial Septal Defect and Murmurs of Organic Tricuspid Stenosis**

*Oldrich Prec, Fredrick Wood, Jr. and Ormand C. Julian, Chicago, Ill.*

The trend toward surgical correction of valvular lesions has recently resulted in re-emphasis on murmurs originating in the tricuspid valve and their differentiation from murmurs originating in the mitral valve. A correlative study was undertaken in 4 patients with atrial septal defect, normal mitral valve, and apical diastolic murmur and in 8 patients with rheumatic tricuspid stenosis. Auscultatory observations and phonocardiograms were correlated with cardiac catheterization data, surgical findings, and autopsy material.

The apical murmur in atrial septal defect, rumbling in quality and late diastolic in timing occurs 0.10 minute after onset of the P wave. It is concluded that it is a right ventricular filling murmur originating from vibrations of an overstretched tricuspid valve or possibly from vibrations of the ventricular wall. An early diastolic pressure gradient is minimal or absent, and only coarse vibrations were recorded during the entire diastolic inflow period. These are increased and the end diastolic murmur disappears if atrial fibrillation is present. The term "hypervolemic murmur of the tricuspid valve" is suggested because (1) there is no evidence of relative stenosis of the tricuspid valve; (2) they disappear immediately after closure of the defect and (3) increased blood flow through the tricuspid valve is their common underlying cause.

Four patients with rheumatic tricuspid involvement had a tight stenosis, another 4 having a moderate stenosis. Two patients with tight stenosis had sinus rhythm and manifested a late diastolic murmur similar in timing to the murmur in atrial septal defect but better heard along the left sternal border. In two patients with atrial fibrillation and tight stenosis, the diastolic murmur began 0.48 to 0.50 minute after the onset of QRS with a short interval between the end of the second sound and the onset of the murmur. The patients with moderate tricuspid stenosis had atrial fibrillation. An early diastolic murmur beginning simultaneously with the second sound was present along the left sternal border with its maximum at the lower sternum. This murmur is synchronous with an early pressure gradient between right atrium and right ventricle. Thus, differentiation from the murmur of aortic regurgitation might prove to be difficult.

**Prevention of Subacute Bacterial Endocarditis: the Concept of Systemic and Local Antibiotic Therapy in the Prevention of Bacteremia Following Extraction of Teeth**

*Robert S. Pressman and I. B. Bender, Philadelphia, Pa.*

Subacute bacterial endocarditis originates following extraction of teeth or other surgical trauma in approximately 65 per cent of all cases. Bacteremia follows the extraction of 2 or more teeth in 83.9 per cent of unselected cases but may occur as frequently as 93.4 per cent in selected cases involving considerable trauma. Bacteria that normally inhabit the mouth, the most common of which is the streptococcus viridans group, have been repeatedly demonstrated to enter the blood stream during and following the extraction of teeth

Post-extraction bacteremia can be prevented by: (1) keeping extraction trauma to a minimum; (2) introducing antibiotics in the *gingival sulcus*, which is the avenue of access for organisms entering the blood stream; (3) the administration of parenteral antibiotics to inhibit the growth of organisms after they have entered the blood stream. Our studies indicate that post-extraction bacteremia and the subacute bacterial endocarditis that may result from it may best be prevented by a combination of all 3 factors as follows: (1) permit the extraction of no more than 1 tooth at a time, and that with a minimum of "rocking" and trauma; (2) the best topical combination of antibiotics is a troche containing penicillin, sulfadiazine and bacitracin; this to be given one-half hour prior to the extraction; (3) the best parenteral antibiotic is a combination of penicillin and streptomycin given 1 hour prior to the extraction. Any one of these methods may be effective alone, but as trauma increases more protection is needed. The antibiotic troches are effective in reducing the incidence of bacteremia following mild trauma and are effective, although to a lesser degree, if the trauma is severe. *Intramuscular Penicillin alone, is effective if the trauma is mild, but is ineffective if the trauma is severe.* The best results are achieved by combining parenteral penicillin and streptomycin with the antibiotic troche and reduce the incidence of immediate post-extraction bacteremia from 83.9 per cent to 17.1 per cent.

Additional factors in the prevention of post-extraction bacteremia are the alerting of physicians and dentists to the dangers involved and the careful questioning of patients for any manifestation of the rheumatic diathesis. Dentists should be cautioned to use a local anesthetic in preference to general anesthesia.

### Experiences with Phenylindanedione in the Management of Acute Myocardial Infarction

*Edward McCall Priest, Detroit, Mich.*

A series of 251 cases of acute myocardial infarction treated during the acute phase with phenylindanedione is reported. All cases treated for less than 48 hours are excluded. The overall recovery rate was 90 per cent. The incidence of thromboembolic complications was 3.5 per cent. Major hemorrhagic complications occurred in only 1.6 per cent of the total cases. Two cases of skin eruption, requiring the immediate discontinuation of the drug were observed. It is our belief that, at present, this is the oral anticoagulant of choice.

### Primary Epicardial S-T Segment Depression: Experimental and Clinical Observations

*Myron Prinzmetal, Rashid A. Massumi, Lois Schwartz, Louis Rakita and Kiyoshi Kuramoto, Los Angeles, Calif.*

Subendocardial injury was produced in 25 dogs in 8 of which the injury was limited to the subendocardium. The S-T segments in direct leads from the involved subendocardium and mid-myocardium were elevated while those in simultaneous leads from the overlying epicardium were isoelectric. Thus, subendocardial ischemia apparently does not produce S-T segment depression experimentally.

S-T segment depression was produced in 37 dogs in association with acute and chronic coronary occlusion with and without hemorrhagic shock. This surface S-T depression appeared usually in "islands" at the periphery of infarcts. Simultaneous recordings from the subjacent subendocardium showed isoelectric S-T segments. Fluctuations in the surface S-T segment from depression to elevation were not reflected in leads from the subendocardium. In both man and dogs endocardial injury caused only slight change in the endocardial S-T segment, while injury in the epicardial layers resulted in marked epicardial S-T segment change. In 11 of 33 clinical cases of myocardial infarction in which detailed precordial ECG explorations were done, isolated "islands" of S-T depression were found either prior to the development of, or subsequent to the subsidence of the acute QRS changes characteristic of the infarction. In 2 surgical cases, corresponding "islands" of surface S-T depression were found at the periphery of infarcts. Since both the clinical and experimental S-T depression appeared in the absence of any S-T segment elevation to which they could have been considered reciprocal, they are called "primary epicardial S-T depression."

"Primary epicardial S-T segment depression" appear in direct leads only from the outer myocardial layers usually in grossly normal tissue. It is evanescent, appearing and disappearing spontaneously and is preceded by an R or RS wave indicative of normal depolarization. These characteristics suggest that it may be due to minor biochemical changes, occurring in the superficial myocardial layers.

### Hypercatecholemia and Cardiac Damage in Renal Insufficiency

*W. Raab, Burlington, Vt.*

Advanced renal insufficiency is regularly accompanied by an elevation of the catecholamine concentration in the blood, presumably due to renal retention, as suggested by diminished urinary catechol excretion. By colorimetry, the average total blood catechols in 51 normal individuals and in 36 cases of uncomplicated essential hypertension were identical. In 38 cases of renal insufficiency they were 139 per cent higher. The not uncommon "false positive" regitine tests for pheochromocytoma in uremic patients may be explained by the presence of excess circulating catechols.

Serums from patients with renal insufficiency produced a marked epinephrine-like effect on the isolated frog heart. Extracts from uremic serum caused S-T depression and death in rabbits.

The average total catechol concentration in the heart muscle of 23 uremic patients was 36 per cent higher than in 72 "normal" hearts. Since the myocardium possesses the ability to trap circulating catecholamines, it seems that the cardiac catechol increase in uremia derives from the augmented blood catechols. Only a fraction consists of epinephrine and norepinephrine. The bulk is composed of other related catechol compounds with altered side chains and, so far, undetermined toxicity. The cardiac norepinephrine of nephrectomized rats is considerably increased according to Hökfelt. In 14 human uremic hearts, we found a rather low norepinephrine concentration while epinephrine whose cardiac toxicity greatly exceeds that of norepinephrine was 33 per cent increased.

The cardiac output and peripheral resistance in renal insufficiency resemble the findings elicited by epinephrine (Koppermann) and the ECG in uremia usually shows the characteristics of catechol-induced myocardial hypoxia. In 5 out of 17 uremic patients, we found adrenolytic drugs effective in temporarily normalizing the ECG, regardless of the blood pressure reaction, while this never occurred in 19 cases of non-uremic essential hypertension.

Catecholamine retention in renal excretory insufficiency and resulting hypercatecholemia appear to constitute a significant pathogenic factor in nephrogenic cardiac pathology.

### Coronary Blood Flow and Myocardial Metabolism in Valvular Heart Disease

*John L. Read, Reno R. Porter, Edward G. Bond and Sarah C. Bradford, Richmond, Va.*

Coronary blood flow was measured in 16 patients with valvular heart disease using the technic of

coronary sinus catheterization and the nitrous oxide method of Kety and Schmidt. In addition, direct analyses were made for myocardial extraction of oxygen, glucose, lactate and pyruvate. Nine patients were studied before and after equivalent exercise. Two were in congestive heart failure.

Coronary blood flow was significantly reduced in the 6 patients with advanced mitral stenosis. The mean flow was 69 cc. per 100 Gm. per minute compared to the normal of 96. The mean flow in 2 patients with combined mitral disease was 77 cc. per 100 Gm. per minute. This was in considerable contrast to the essentially normal mean flow of 103 cc. per 100 Gm. per minute in the patients with aortic valve disease. The mean cardiac index was 2.27 in mitral stenosis, 2.33 in combined mitral lesions and 3.86 in aortic disease, compared to the normal of 3.12 liters per minute per $M^2$.

In the combined group, the myocardial glucose extraction was higher than the normal for a given arterial level. No significant deviation from the normal was observed in the lactate pyruvate extraction. Lactate extraction varied inversely as the glucose. Work and energy utilization were considerably increased in aortic valve disease and reduced in mitral disease. Mean efficiencies, however, were only slightly reduced. Response to exercise was variable. Coronary blood flow was considerably increased, slightly increased or actually decreased. A limited response was particularly apparent in the older patients. One patient with mitral stenosis and 2 with aortic stenosis developed chest pain during exercise. One patient with aortic stenosis and heart failure responded to exercise, primarily by increasing his coronary flow. His counterpart with aortic insufficiency responded with only a small increase in coronary flow and a large increase in oxygen extraction. Since myocardial oxygen extraction is presumably proportional to stretch, this is compatible with the picture of predominant hypertrophy in aortic stenosis and predominant dilatation in aortic insufficiency.

**The Syndrome of Acute Idiopathic Pericarditis Simulating Acute Surgical Abdomen**

*John L. Read, Paxton P. Powers and Reno R. Porter, Richmond, Va.*

In Jan. 1955, the authors reported a series of patients with acute idiopathic pericarditis in whom abdominal symptoms represented the initial and only manifestations. These symptoms focused attention on the abdomen as the primary site of disease. In several instances the findings became so severe that a surgical abdomen was felt to be present. In 2 cases, the abdomen was actually explored and in another the surgeon's knife was stayed at the last moment by a migration of pain to the precordium, simultaneous with the appearance of an audible pericardial friction rub and a subsequent ECG characteristic of acute pericarditis. In every patient in whom operation was deferred, the pain eventually shifted to the chest with the appearance of a pericardial friction rub. This occurred in from 1 to 3 days. The rub usually reached its maximum intensity in 5 to 10 days and then gradually waned. With the shift of pain, the abdominal symptoms invariably underwent a rapid amelioration. The constitutional symptoms were more severe than those seen in the usual case of acute idiopathic pericarditis and were more often associated with a significant leukocytosis. Of 8 patients with the typical picture of idiopathic pericarditis, only 2 presented a significant leukocytosis on admission. Both of these patients also had a small pleural effusion. Of 7 patients with predominant abdominal manifestation, 5 had a significant leukocytosis. In fact, those subjected to surgery had the most marked leukocytosis. A recent patient with this syndrome underwent an exploratory laparotomy. He was found to have a mesenteric lymphadenitis. This suggests the possibility of a common viral etiology for mesenteric lymphadenitis and acute idiopathic pericarditis, at least in those patients whose initial manifestations are centered in the abdomen. Studies are being carried out in order to determine whether a common etiology does exist.

**Distribution of Cardiac Conduction Tissue**

*Jane Sands Robb, Syracuse, N. Y.*

The distribution of conduction tissue in the heart is used in the explanation of the ECG. Until now, studies of the comparative histology and distribution of this tissue have not been evaluated in the analysis of differences in the ECGs of various species. For instance, some claim that this system is neomorphic in birds and mammals. In selachians, amphibians and reptiles, the muscle fibers are said to be the pathway of conduction. Then, in these animals, how can one explain the presence of P, Q, R, S and T waves which may be similar to those of mammals and birds?

ECGs were taken of various species and, thereafter, serial sections of the entire hearts were prepared. Specialized tissue was identified and reconstructions made. All mammals have grossly similar systems, though there are some variations in length, diameter and position of the various portions. Birds have a complex dual system. Selachians, amphibians and reptiles have specialized tissue which is found in certain homologous locations but which is not condensed into the more compact tracts seen in birds and mammals.

If this tissue is the conduction pathway and if penetrating electrodes pick up potentials from the ensheathed pathways, one would expect to find the basal septal area, activated earlier than the apical septal area, which is not the case, according to some reports. The main bundle in birds and mammals is

composed of isolated tracts of various diameters, interspersed with nerves and ganglions. We do not know that these many tracts are activated exactly simultaneously, nor do we know that the conduction rates are identical. Some recent physiologic studies are best explained on the basis that conduction rates vary within the system.

**Heart Pain—Mechanisms and Relief**

*Joseph T. Roberts, Buffalo, N. Y.*

The variable clinical picture of heart pain is explained by our finding that nerves need a blood supply for normal functions and that pain, pressure, touch, temperature, position sense, motor and autonomic fibers are variably affected by local reflex ischemia. These studies show that the *vasa nervorum* in the left arm of animals contracted after ligation of a coronary artery and that after release of the ligature, reopening of the *vasa nervorum* takes place. The vasa nervorum in the right arm of animals did not change after coronary ligation. This lends strong support to our theory that cardiac referred pain is due to ischemia of the somatic chest or arm nerves with vasospasm of their vessels. We have seen opening or closing of vessels in nerves with appropriate drugs or other stimuli. This appears to support the mechanism as it accounts for: (1) referral of pain; (2) relief of angina at times by drugs or local anesthesia or revascularization; (3) the occasional silent infarction; (4) the occasional disappearance of angina after infarction; (5) the shoulder-hand syndrome or Dupuytren's contracture frequently observed following myocardial infarctions and (6) the influence of psychic or stress situations in the precipitation of angina. Cardiac muscle hypertrophy reduces the heart's blood supply but usually does not cause pain in the absence of other causes, because the myocardial nerve endings remain close to their capillaries despite ischemia of muscle fibers. The high frequency of post-coronary onset of Dupuytren's contracture and variants of the shoulder-hand syndrome has been used as an "alerting sign" for study, which has revealed some cases of unrecognized myocardial infarction.

We show the need to stress the summation of multiple predisposing and precipitating causes to avoid errors in finding and handling people with heart pain. Patients with heart pain have tried to show their varying sensations with the use of implements which pictorialize their complaints graphically in color and these are shown in relation to the neuroanatomy involved. Relief of heart pain is improved by many methods besides drugs and surgery and these results are explained in view of our studies on the *vasa nervorum*. Group therapy of heart-pain subjects is shown as a great help in handling these people.

**Physiologic Effects of Long-Term, High Dosage Estrogen Therapy on Adrenocortic, Testicular and Thyroid Function in Coronary Atherosclerosis**

*R. W. Robinson, N. Higano, W. D. Cohen, R. C. Sniffen and J. T. Sherer, Jr., Worcester, Mass.*

Previous investigators have demonstrated favorable alterations of the serum lipid pattern with estrogen therapy in human atherosclerosis. We are reporting the effects of estrogen on various endocrine functions, when given on a long-term basis and in large dosage to men.

Twenty middle-aged males with myocardial infarction were studied before and at intervals after initiation of therapy with 5 to 25 mg. daily of oral mixed, conjugated equine estrogens (Premarin). Twenty male controls with myocardial infarction received placebo tablets.

After a routine clinical evaluation the serum cholesterol, phospholipide and cholesterol content of the $\alpha$- and $\beta$-lipoproteins (separated by paper electrophoresis) were determined. Urinary 17-ketosteroids were fractionated by gradient elution chromatography on alumina after hydrolysis of conjugates by $\beta$-glucuronidase plus acid. Testicular biopsies, obtained under local anesthesia, were studied by conventional and histochemical technics. Thyroid function was estimated by the 24-hour uptake of tracer doses of $I^{131}$.

Statistical analysis of the serum lipid data revealed significant lowering of cholesterol, increase of phospholipids, progressive decrease of the cholesterol to phospholipid ratio and decrease in the ratio of $\beta$- to $\alpha$-lipoprotein cholesterol. Most of these changes were initiated early in therapy. Urinary 17-ketosteroid excretion studies have shown a striking increase in dehydroepiandrosterone, essentially unchanged excretion of 11-oxygenated 17-ketosteroids, and large parallel decreases of androsterone and etiocholanolone during estrogen therapy. Serial testicular biopsies have shown uniform hypospermatogenesis after 1 month and atrophy of tubular and Leydig cells after 12 months of therapy. A study of thyroid function before and after 12 months revealed no significant changes as measured by the uptake of tracer doses of $I^{131}$. The clinical, biochemical and endocrinologic significance of these data is discussed.

**Muscular Contraction in the Infundibular Region as a Mechanism of Pulmonic Stenosis and of Bidirectional Shunting through Ventricular Septal Defects in Man**

*Simon Rodbard and Aaron Shaffer, Chicago, Ill.*

Analysis of the pressures obtained during cardiac catheterization in the right ventricle and in the infundibular chamber made it possible to differ-

ntiate two types of infundibular stenosis. In 3 of 13 ases, simultaneous pressure peaks in right ventricle nd in infundibulum suggested that the stenotic esion between these chambers was of fixed cross- ection area throughout systole. The "band" type f infundibular stenosis may be an anatomical ounterpart of this fixed lesion. By contrast, in the emaining 10 cases, pressures in the two chambers egan to rise together during isometric contraction nd for a variable part of the rapid ejection phase, usually 0.1 seconds), but the infundibular pressure hen began to fall, even though the right ventricular ressure continued to rise. The two pressures did not ecome coincident again until the end of ejection. These findings can be best explained by an in- undibular stenosis which becomes reduced in cross- ection after ventricular systole has commenced. Phylogenetic and ECG evidence suggests that the infundibular portion is one of the last portions of the right ventricle to become activated during systole. The data of the 10 cases presented may be taken as evidence for the dynamic narrowing of this outflow tract during early or mid-systole, probably due to muscular contraction in this region. A tunnel type of infundibular stenosis might be expected to produce such an effect, and this was demonstrated at surgery in one of our cases. Differentiation of these two forms of stenosis may have importance in the surgical approach to a case.

In the presence of a ventricular septal defect, the foregoing dynamic sequence may well be a factor in the production of the frequently observed bidirectional shunts. In early systole, shunt flow would tend to be from left-to-right. Then contraction at the infundibular region produces an increased resistance to pulmonary flow, decreasing the shunt or even reversing it.

**The Characteristics of Non-Fatal Myocardial Infarction in the Aged**

*Manuel Rodstein, New York, N. Y.*

Approximately 700 ambulatory residents over the age of 60 years at The Home for Aged and Infirm Hebrews of New York were studied for evidence of non-fatal myocardial infarction over the period 1951 to 1955. A total of 47 cases of presumptive myocardial infarction were found and these were divided into 3 groups.

The first or silent group consisted of 14 cases without symptoms of any type referable to the cardiovascular system. Ten persons were over 71 years old. Eight had blood pressures consistently elevated above 150/90. They were all diagnosed in retrospect by ECG changes in routine annual tracings without any history of significant intercurrent illness. In all but one, progressive ECG changes, significant fall in blood pressure, leucocytosis, fever and elevation of the sedimentation rate were absent.

The second or atypical group consisted of 20 cases without anterior chest or upper extremity pain, pressure or burning, but did have symptoms of dyspnea, syncope, dizziness, nausea and mid or lower abdominal pain. Sixteen were over 71 years of age. Fifteen had blood pressures consistently elevated above 150/90. In all but one case, the symptoms were attributed to congestive heart failure, pneumonia, cerebral or abdominal disease prior to ECG diagnosis. Twelve had fever, leucocytosis and elevation of the sedimentation rate; sixteen had serial ECG changes and only one had a significant fall in blood pressure. This group had the highest incidence of preceding cardiac enlargement, ECG abnormality and mental deterioration.

The third or typical group consisted of 13 cases with anterior chest or upper extremity pain, or the symptoms of pressure or burning. They were all correctly diagnosed. Eleven were over 71 years old and had blood pressures consistently elevated above 150/90. Almost all had serial ECG changes, fever, leucocytosis and elevation of the sedimentation rate and 8 had a significant fall in blood pressure.

The observations indicate a high incidence in the ambulatory aged of silent and atypical myocardial infarction of a relatively mild degree of clinical severity. Periodic ECG study of apparently well, elderly individuals is indispensable for clinical detection of asymptomatic myocardial involvement.

**Responses to Complete Right Ventricular Failure in Dogs Maintained with a Mechanical Left Ventricle**

*John C. Rose and Herbert P. Broida, Washington, D. C.*

A pump with controlled output was used to replace the left ventricle in dogs. Blood was drained into a reservoir from the left atrium and pumped into the aorta. The right ventricle continued to function effectively, keeping pace with the output of the pump. Central venous pressure remained normal, rising slightly with increases in flow.

Complete right heart failure was produced by inducing ventricular fibrillation; left ventricular output remained constant. Depletion of the pump reservoir occurred immediately due to reduction of flow from the right heart. Simultaneously, a marked elevation of central venous pressure (CVP) (average 21 mm. Hg) and fall in pulmonary arterial pressure occurred. Systemic arterial pressure remained unchanged. It was necessary to add fluid (average 2.5 L. gelatin or saline) to attain an equilibrium at which the return flow to the pump equaled its output and at which pulmonary arterial presure (PAP) returned to pre-failure levels. Central venous pressure (CVP) then became a linear function of pump output rising to an average of 50 mm. Hg at flow rates of 3.5 L. per minute.

With increases in pump output, the animal removed portions of the reservoir volume, the average increment being 500 cc. for each liter per minute increase in flow. Flow decreases did not return fluid to the reservoir. Red blood cell and albumin tracer technics revealed that there was some increase in intravascular plasma volume but the major portion of the fluid volume added to the circulation with the induction of fibrillation and with flow changes left the intravascular compartment rapidly.

These observations suggest that the right ventricle plays an active role in the maintenance of normal intravascular pressures. Extreme elevations of central venous pressures are necessary for maintenance of the circulation by the left ventricle alone and are directly proportional to flow rate. In this experimental system, acute edema formation seems closely interrelated with venous hypertension.

**Surgical Closure of Patent Ductus Arteriosus Associated with Pulmonary Hypertension in Infants and Children**

*George G. Rowe, John F. Brown, John H. Huston, Herman Tuchman, George M. Maxwell, Arvin B. Weinstein, Wm. P. Young, Anthony R. Curreri, Joseph W. Gale and Charles W. Crumpton, Madison, Wis.*

A series of 11 children, ranging in age from 11 weeks to 11 years (7 were 13 months or less) with large patent ducti arteriosi and pulmonary hypertension, were operated on by surgical closure of the ductus in each case. Ten cases were diagnosed by cardiac catheterization and one by angiocardiography. Preoperative pulmonary artery pressures averaged 87 per cent of the aortic pressure and total pulmonary resistances averaged 1998 dynes per cm.$^{-5}$ per sec., 59 per cent of total systemic resistance. In 2 cases there was a significant oxygen desaturation in the femoral artery as compared with the brachial artery, indicating reversed flow through the ductus. Pulmonary arterial and aortic blood pressures were measured directly at the time of operation, before, during, and after temporary occlusion of the ductus. In 7 of 11 patients the mean pulmonary arterial pressure fell (average of these 7 was −15 mm. Hg) and in 8 of 11, the mean aortic pressure rose (average of these 8 was +20 mm. Hg) when the ductus was occluded. The others showed no pressure change.

Four of these patients died postoperatively. Three had associated major congenital cardiac defects and one was a cretin. The 3 with associated cardiac defects showed no pulmonary artery pressure change when the ductus was occluded and apparently died from their uncorrected defects. Ventricular septal defect was the most common unrecognized associated anomaly.

Elevated pulmonary vascular resistance was no contraindication to surgery in this series and this experience suggests that the isolated patent ductus regardless of size or pulmonary arterial pressure may be occluded safely in this age group. The aortic and pulmonary pressure response to ductus closure may be a helpful prognostic guide.

**Treatment of the Low Salt Syndrome in Congestive Heart Failure Using Mercurial Diuretics**

*Albert L. Rubin and Warren S. Braveman, New York, N. Y.*

The production of the low salt syndrome in cardiac patients with refractory congestive heart failure is generally attributed either to fluid retention with electrolyte dilution or to excessive salt loss, induced by the frequent administration of mercurial diuretics. In our experience, the former is the important etiologic factor in the production of this syndrome and might better be termed the "dilution syndrome."

Adequate evidence to incriminate mercurial diuretics is not available. In order to state that hyponatremia results from the use of a mercurial agent, one must demonstrate that the urinary sodium concentration, following drug administration, exceeds the plasma concentration of sodium, in a setting where fluid intake has been restricted to approximate the patient's insensible water loss. To our knowledge, this has never been demonstrated.

In a prior study of a group of 25 refractory cardiac patients with normal plasma electrolyte patterns, a hyperchloremic acidosis was produced to restore a responsiveness to mercurial diuretics. During the mercurial-induced diuresis that followed, the urinary sodium concentration was significantly lower than the plasma sodium concentration in all instances. From these observations, a method of treatment of the low salt syndrome, utilizing mercurial diuretics seemed feasible.

Two cardiac patients with congestive failure and refractory fluid retention were the subjects for this study. These patients also had azotemia, oliguria, anorexia with nausea and a marked hyponatremia and hypochloremia. The response to mercurial diuretics was restored in these subjects by the production of a hyperchloremic acidosis using Diamox and ammonium chloride. No attempt was made to alter the low plasma sodium concentration (117 mEq. per L.) by the administration of hypertonic saline solution. In the setting of hyponatremia and hyperchloremic acidosis, the daily administration of mercuhydrin resulted in a marked and sustained diuresis, during the course of which the plasma sodium concentration returned to normal (138 mEq. per L.). Striking clinical improvement occurred thereafter.

**Irreversible Depression of Rat Heart Adenosinetriphosphatase Activity by Quinidine**

*Arthur Ruskin, Galveston, Tex.*

Cardiac depression by quinidine has a biochemical basis. Oxygen consumption, succinic dehydrogenase activity, glucose and pyruvate oxidation, anaerobic glycolysis and adenosinetriphosphatase (ATP-ase) activity are all depressed. The following experiments deal with the effects of quinidine upon the ATP-ase activity of rat heart homogenates and the attempted reversals of these effects by ascorbic acid, cysteine, glutathione and BAL.

Significant ($P < 0.01$) depression of ATP-ase activity ($\mu$g of Ph per mg. per hour) of at least 35 per cent resulted from quinidine sulphate (final concentration $7.5 \times 10^{-4}$). Ascorbic acid and the above sulfhydryl compounds themselves had no significant effect ($P > 0.5$) upon the ATP-ase activity. None of them prevented or reversed quinidine-induced depression of the ATP-ase activity ($P > 0.1$). By contrast, mercurial inhibition of the ATP-ase of the rat heart and kidney is reversed by all 4 of these compounds.

In preliminary experiments, procaine and procaine amide, clinical substitutes for quinidine, in concentrations as high as $7.5 \times 10^{-3}$ indicate little or no inhibition of rat heart ATP-ase activity.

**Effects of Tobacco on the Cardiovascular System**

*Henry I. Russek and Burton L. Zohman, New York N. Y.*

The response to smoking cigarettes was studied in 96 subjects of whom 42 were normal and 54 were patients with coronary disease. All of the normal subjects were habitual smokers, ranging in age from 21 to 60 years. Twelve of this group had complained of persistent precordial discomfort for which they had sought medical aid. The remaining 30 were selected from a group of healthy persons because on interrogation they related symptoms of cerebral, cardiac or gastrointestinal origin as a result of smoking. A significant increase in heart rate and blood pressure was observed following the smoking of a regular cigarette in both normal subjects and patients with coronary heart disease. Significant ECG alterations were observed in more than two-thirds of the normal persons with symptoms referable to smoking. Constant abnormalities in the ECG and BCG were found in a number of the hypersensitive normal subjects, while smoking their usual daily quota. The existence of "tobacco heart" was confirmed as a definite clinical entity. Denicotinized cigarettes caused less disturbance of the heart and created fewer side effects than did ordinary brands. Nitroglycerin was ineffective in blocking the action of nicotine. The main effects of tobacco on the cardiovascular system of hypersensitive normal subjects do not appear to be due to coronary vasoconstriction but rather to direct myocardial action and/or the effect of nicotine on cardiac ganglions.

More than half of the patients with coronary disease showed deterioration in ballistic pattern following the smoking of a regular cigarette. Denicotinized cigarettes showed no superiority over regular brands as measured by the BCG in patients with coronary disease. The use of various drugs in an attempt to block the nicotine response led to the conclusion that the latter is based primarily on peripheral vascular constriction and not on alterations in coronary blood flow. However, other cardiovascular, local and systemic effects of smoking clearly establish the inadvisability of the continuance of this habit in patients with heart disease.

**Long-Acting Coronary Vasodilator Drugs: Metamine, Paveril, Nitroglyn and Peritrate**

*Henry I. Russek and Burton L. Zohman, New York, N. Y.*

Although glyceryl trinitrate is unexcelled prophylactically when employed prior to contemplated exertion in angina pectoris, the relatively short duration of its action does not afford prolonged protection for the patient afflicted with this disease. The search has therefore continued for a long-acting coronary vasodilator which is capable of reducing the frequency and severity of anginal attacks by routine daily administration. Many drugs have been characterized by their individual sponsors as fulfilling this need but few have been able to withstand the test of time and clinical usage. The most popular of the agents now undergoing clinical trial are Metamine (triethanolamine trinitrate biphosphate), Paveril (dioxyline phosphate), Nitroglyn (coated granules of glyceryl trinitrate) and Peritrate (pentaerythritol tetranitrate).

The present study has attempted to assess the relative and absolute value of each of these agents in the treatment of angina pectoris by recording their respective actions on the ECG response to standard exercise (Master two-step test) in 21 carefully selected patients. Employing this technic, it was found that Metamine and Paveril produced little or no significant effect on exercise response as measured by the ECG. Nitroglyn, in spite of the logic behind its use, gave disappointing results and was found to be relatively inert in the dosage of one-twenty-fifth of a grain. With larger doses ($^2/_{25}$ to $^4/_{25}$ grain), Nitroglyn evoked slight to moderate improvement in exercise response for a period of 6 hours following its administration in almost two-thirds of the patients tested. Peritrate showed a marked modifying influence on the ECG recorded after exercise in 14 of the 21 patients tested. The effect of this agent was comparable to that of glyceryl trinitrate but its action, after a latent period of 60

to 90 minutes, could be demonstrated as long as 5 to 6 hours following the administration of a therapeutic dose.

Of the 4 drugs tested, only Peritrate appears worthy of the designation "long-acting coronary vasodilator." Peritrate appears to satisfy the need for prolonged coronary vasodilatation in most patients with angina pectoris.

### Coronary Artery Pressure and Contractile Strength of the Right Ventricle in Dogs

*Peter F. Salisbury, Los Angeles, Calif.*

In order to increase the metabolic support of the right ventricle, Fineberg and Wiggers (in 1936) suggested that predominantly right sided heart failure should be treated with pressor agents. This has not been investigated or applied clinically; the currently accepted standard management of cardiac failure does not distinguish between failure of the right ventricle or left ventricle.

In dogs, the right ventricle was challenged by graded compression of the pulmonary artery with a hydraulic clamp. Coronary artery pressure and, therefore, coronary flow to both ventricles was modified by arterial blood reservoirs, by a clamp on the ascending aorta, by an intra-aortic distensible bag and by pressor agents. A direct relationship was found between the coronary artery pressure and the maximum systolic pressure of the challenged right ventricle. Irreversible failure of the right ventricle was consistently relieved by an increase of the coronary artery pressure. When the coronary artery pressure was maintained at normal levels the right ventricle did not fail in spite of maximal pulmonary artery compression.

The application of this principle to patients with cor pulmonale and with other forms of right ventricular strain is obvious. Such investigations are now being conducted.

### P Vector Loop in Health and Disease as Studied by the Technic of Electric Dissection of the Vectorcardiogram (Differential Vectorcardiography)

*Toyamo Sano, H. K. Hellerstein and Eugene Vayda, Cleveland, Ohio.*

The development of a practical apparatus to dissect the vectorcardiogram has made it possible to study the fine details of the component loops of the vectorcardiogram. The present study consists of 79 cases where isolated P vector loops were obtained by this new technic. There were 16 normal cases, 15 practically normal, 26 with left atrial hypertrophy, 15 with right atrial hypertrophy, 3 with combined atrial hypertrophy and 4 cases with ectopic origin of the P wave. The cube reference system was employed.

Exclusive of the P vector loops of ectopic origin, the direction of inscription of the P vector loop in health and disease is principally counterclockwise in the frontal and horizontal planes, and clockwise in the sagittal plane. The normal P loop is small, closed or slightly open, and directed almost vertically inferiorly, slightly anteriorly. The P loop of left atrial hypertrophy is larger, open, bizarre, bifid or with a figure-of-8 configuration, with a larger maximum vector formed by the terminal portion of the loop, which is directed posteriorly, inferiorly and leftward. In right atrial hypertrophy, the P loop tends to form one plane, unlike normal and left atrial hypertrophy loops. In right atrial hypertrophy the loop is the largest, usually open and the maximum vector is formed by the first portion of the loop which is directed anteriorly and somewhat inferiorly. In combined atrial hypertrophy there are large early anterior and large late posterior leftward forces. The Ta vector is located about 180 degrees from the maximum P vector in hypertrophy.

The morphology of the P vector is readily related to the anatomic location of the hypertrophied atrium. The superiority of the isolated P vector loop lies in the ease with which deviations from the normal pattern are detected.

### Incidence and Prevention of Ventricular Fibrillation in Hypothermic Dogs

*Everton M. Santos, Evans L. Frederickson and C. Frederick Kittle, Kansas City, Kan.*

The incidence and prevention of ventricular fibrillation was studied under standard conditions in 5 groups of hypothermic dogs (25 C.). In all groups the animals were anesthetized with intravenous Nembutal, were connected to an automatic respirator and then cooled by immersion in ice water. An ECG was connected to the animals and tracings taken whenever indicated. At a temperature of 25 C. or less, right thoracotomy was done, inflow and outflow occlusion established and the incidence of ventricular fibrillation noted at subsequent right ventriculotomy. In the first 2 groups, arterial blood samples were taken at the time of thoracotomy and at the time of fibrillation, if the latter occurred. These samples were analyzed for oxygen and carbon dioxide content, and the pH was measured.

In group 1, no drugs were given. Ventricular fibrillation at the time of right ventriculotomy or shortly thereafter occurred in 5 of the 11 dogs. In group 2, neostigmine (0.25 mg.) was injected into the coronary circulation after total occlusion of the circulation. In 10 dogs with definite neostigmine effect (bradycardia), 5 had ventricular fibrillation. In group 3, calcium gluconate (100 mg.) was injected into the coronary circulation after total

eclusion of the circulation. Ventricular fibrillation ecurred in 6 of these 11 animals, immediately llowing the injection of calcium. The other 5 had ight ventriculotomy without developing ventricular brillation. In group 4, large doses of neostigmine 1 mg.) were given in an attempt to produce cardiac rrest. In 4 dogs so treated, the heart did not stop, lthough the rate went as low as 3 per minute. All 4 nimals developed ventricular fibrillation with ight ventriculotomy. In group 5, Flaxedil was iven by the same technic of coronary perfusion in a losage of 1 mg. or 0.5 mg. per Kg. of body weight. 3 of the 9 animals developed ventricular fibrillaion, 1 dog before the ventriculotomy was done. This group exhibited the most profound changes in he ECG, following injection of the drug.

The arterial blood samples showed normal oxygen values in all determinations, normal or decreased carbon dioxide content and moderately increased pH values. It is concluded that neostigmine, calcium gluconate and Flaxedil administered by coronary perfusion do not exert any prophylactic action against ventricular fibrillation in the hypothermic animal.

### Epidemiology of Rheumatic Fever in Miami, Florida

*Milton S. Saslaw and Murray M. Streitfeld, Miami, Fla.*

The epidemiologic pattern of group A β hemolytic streptococci has been studied for the past 3 years in an effort to clarify the relationship of this group of organisms to rheumatic fever in this area. This study was prompted by observations that the disease is less frequent in native Floridians, acute episodes tend to subside rapidly when patients migrate to this area and attacks, originating here, are usually very mild and of short duration.

Monthly throat cultures were taken from an average of 315 children (total of 741 cultures) attending the first 3 grades in 3 Miami schools from 1953 through 1955. Approximately 50 per cent of these children were found to harbor group A streptococci at least once a year. These findings were confirmed in 1200 additional children attending 48 other schools.

The recovered streptococci generally evoked a systemic response, as evidenced by significantly increased antistreptolysin O titer levels in children with typable or nontypable group A, group C and/or group G streptococci. Streptococcal recovery rates did not appear to vary with economic status, race or age. Group C streptococci were more common and the average antistreptolysin O titer was higher among Negro children. None of the children developed either overt rheumatic fever or glomerulonephritis during the 3-year period, although no prophylaxis was given. The concept that the presence of group A β hemolytic streptococci in the throat is almost always diagnostic of streptococcal infections and that 3 per cent of these develop rheumatic fever, does not apply in Miami.

### The Significance of Albuminuria in Congestive Heart Failure: A Clinicopathologic Study

*Charles H. Scheifley, George A. Race, Otto P. Schumacher and Jesse E. Edwards, Rochester, Minn.*

Two hundred and twelve necropsy cases of congestive heart failure of various types were divided into 2 groups. Group 1 consisted of 161 cases in which the kidneys were histologically normal or contained minor lesions not thought to be responsible for albuminuria. Group 2 included cases in which there were renal lesions of such a nature that they themselves could have been considered responsible for albuminuria. A gradation of the degree of heart failure and a microscopic study of the kidneys were done in all cases. Albuminuria was present in 88 per cent of group 1 cases and in 96 per cent of group 2 cases. A good correlation was found between the grade of albuminuria and the grade of heart failure. It was observed that grade 4 albuminuria could exist in patients with congestive heart failure who had histologically normal kidneys. Conversely, severe heart failure can be present at times without albuminuria. Surprisingly, hypertensive heart disease (diffuse arteriolar disease), as compared to mitral stenosis, was not associated with a significantly increased occurrence of albuminuria.

A correlation also existed between the grade of albuminuria and the grade of hypertension as determined on the basis of fundiscopic examination. There was no correlation between the grade of albuminuria and the systolic or diastolic levels of blood pressure, the known duration of increased blood pressure, the grade of hematuria, the level of the blood urea, or the grade of bromsulphalin retention.

A study was also made of the clinical records of 136 patients having chronic constrictive pericarditis. The degree of albuminuria was correlated with the various factors listed above and with the level of the venous pressure. (Insufficient necropsy material precluded pathologic evaluation of the kidneys.) The most important conclusion from this group of cases was that, although the congestive factor (retention of fluid) could be great, the degree of albuminuria was never greater than in grade 1 or 2. This finding has been of considerable clinical value in rapid elimination of chronic constrictive pericarditis in the differential diagnosis of the various diseases with which it may be confused, namely

nephrosis, other forms of heart failure and other edema-producing syndromes.

**The Spatial Vectorcardiogram and Electrocardiogram in Mitral and Aortic Valvular Disease**

*Leonard Scherlis, R. Adams Cowley, Aubrey Richardson, Charles Adams and William S. Love, Baltimore, Md.*

Spatial vectorcardiograms were recorded by the cube technic in 41 patients with rheumatic heart disease who underwent commissurotomy. The spatial vectorcardiograms were correlated with right ventricular pressures, operative findings and ECGs which included routine 12 leads and $V_3R$. The ECGs were analyzed in detail, using the standard criteria for the diagnosis of right ventricular hypertrophy.

In 26 of the 41 patients who were subjected to mitral commissurotomy, there was minimal or no mitral regurgitation found at surgery. Two patients had accompanying interatrial septal defect which had been diagnosed preoperatively, and one had an anomalous pulmonary vein. There were complicating aortic lesions of varying degrees or significant mitral regurgitation in 12 others. There was ECG evidence of right ventricular hypertrophy in 15 patients with pure mitral stenosis and vectorcardiographic evidence of right ventricular hypertrophy in 20 patients. The increased right ventricular pressure was reflected in the proportionate displacement of the vectorcardiogram anteriorly and to the right. In 4 patients in whom significant degrees of mitral regurgitation were found, there was a marked increase in right ventricular pressure and electrof cardiographic and vectorcardiographic evidence o right ventricular hypertrophy.

The ECG and vectorcardiographic criteria of right ventricular hypertrophy are discussed on the basis of the above experience. Vectorcardiograms were recorded on an additional 35 patients with predominant aortic valvular lesions. The ECGs and vectorcardiograms were analyzed for evidence of left ventricular hypertrophy. In the absence of conduction delays, the vectrocardiograms of 14 patients were displaced posteriorly and to the left and inscribed in a clockwise direction in the horizontal plane rather than counterclockwise. In 6 patients, left ventricular hypertrophy was diagnosed on the basis of vectorcardiographic criteria, but, was absent on the basis of ECG criteria. Evidence for the additional value of spatial vectorcardiography as a supplementary aid in the evaluation of right, left and combined ventricular hypertrophy is presented in further detail in relationship to mitral and aortic disease.

**Neurogenic Factors in Coronary Disease. Experimental Findings and Clinical Results of Selective Vagotomy**

*Sidney Scherlis and R. Adams Cowley, Baltimor, Md.*

Clinical observations have suggested that neurogenic factors are important, not only in causin episodes of angina pectoris, but in precipitatin coronary occlusion in persons predisposed by reaso of arteriosclerosis. Because of this, experiment were carried out in dogs to clarify the mechanism involved. The thoracic vagus and its branches an the stellate ganglion were stimulated electrically i anesthetized open-chest dogs. The results wer striking and consistent: by stimulating certai cardiovagal branches on the left one could repeatedl produce electrocardiographic changes strongl resembling acute coronary occlusion in humans where T waves were upright initially, S-T becam elevated and coved, T higher, followed by symmetrical inversion of T and return of S-T to the baseline. Many arrhythmias were produced, including ventricular fibrillation and death. In contrast, stimulation of stellate ganglion produced a pattern suggesting coronary insufficiency in humans: where T was upright, S-T became depressed and T became high, sharp and symmetrical.

The practicality of severing the cardiovagal branches in humans was determined. Four patients with severe angina pectoris, after not being improved by accepted methods of medical treatment, were selected and operated upon. In 3 patients, the angina was greatly improved, in the fourth partially so. These results, experimentally and clinically, emphasize neurogenic and dynamic rather than static arteriosclerotic factors alone in coronary disease. It may be that the eventual approach in patients, severely incapacitated by angina may be twofold, selective vagotomy to remove possible vasoconstrictor influences and a revascularization procedure to add new vessels.

**Rheumatoid Spondylitis and Aortic Insufficiency**

*Donald P. Schilder, W. Proctor Harvey and Charles Hufnagel, Washington, D. C.*

The relationship of rheumatoid spondylitis (Marie-Strumpell arthritis) to heart disease is of current interest. It is not a common disease and, therefore, the relationship to cardiac disease, particularly of the aortic valve, has not been clearly defined. We have had the opportunity to study a large number of patients with aortic insufficiency, and have noted a surprisingly high incidence of rheumatoid spondylitis.

Some unusual features, not previously described are: (1) five per cent of 100 cases with aortic insufficiency had rheumatoid spondylitis; (2) these 5

patients had severe heart disease and three died of it; (3) all had far-advanced rheumatoid spondylitis which had recently required treatment, and they all had elevated sedimentation rates and 2 had anemia; (4) only one had a history of rheumatic fever, and one had a history of peripheral rheumatoid arthritis; (5) none had a history of syphilis or a positive serology; (6) the physical, ECG and x-ray findings were remarkably similar and revealed free aortic insufficiency, marked left ventricular hypertrophy, first degree heart block and far advanced rheumatoid spondylitis.

The cases differ from those previously reported in that rheumatic fever and peripheral rheumatoid arthritis were not common and the heart disease was not benign. Because of this apparent high incidence of rheumatoid spondylitis in patients with severe aortic insufficiency, it is proposed that a direct relationship must exist between them.

**Clinical Evaluation of Sinthrom, a New 4-Hydroxycoumarin Anticoagulant**

*Fred J. Schilling and Oscar R. Kruesi, New York, N. Y.*

Since the introduction of Dicumarol, there has been a constant search for a 4-hydroxycoumarin derivative which would show greater safety and effectiveness in thromboembolic disorders. The most recent member of this group to be found clinically useful is Sinthrom, a brand of acenocoumarin (nitro-phenyl-acetyl-ethyl-4-hydroxycoumarin). Sixty-five patients, (representing 1762 patient days at an average of 27 days per patient) are the basis for the clinical evaluation of this drug.

The initial single oral dose was 20 mg. on the first day. However, patients, showing evidence of hepatic dysfunction, cardiac or renal insufficiency or malnutrition, received a smaller dose. Initially, 48 of the 65 patients received 20 mg. of Sinthrom and 8 to 16 mg. on the second day. In general, the second dose could be estimated with some degree of accuracy from the response of the prothrombin time to the initial dose. The average dose required to maintain the therapeutic range was between 4 and 6 mg. per day.

Of the 65 patients, fifty-five (85 per cent) with thromboembolic disorders were within the therapeutic range of hypoprothrombinemia in 48 hours or less after the initial dose of Sinthrom. Five patients developed therapeutic hypoprothrombinemia between 12 and 24 hours after the initial dose. These 5 patients continued to show greater than average sensitivity to the drug during the maintenance period. Three out of the 65 patients received vitamin K or $K_1$ preparations for treatment of excessive hypoprothrombinemia, although only 1 of the 3 had any evidence of bleeding (epistaxis).

All patients developed adequate hypoprothrombinemia from Sinthrom. The single oral daily dose administration is adequate to produce and sustain hypoprothrombinemia. Sixty-five patients on single daily doses of Sinthrom were within the therapeutic range approximately 75 per cent of the time. It is noteworthy that this drug was mainly administered by the medical house staff, none of whom had had extensive experience with anticoagulant therapy. After cessation of Sinthrom, the dilute plasma prothrombin time rapidly approached normal within 30 hours. There was no evidence of intolerance to the drug as judged by clinical and laboratory observations. In our experience, Sinthrom appears to have certain advantageous characteristics, effectiveness in small doses, absence of intolerance and ease and safety of maintaining therapeutic anticoagulation.

**Observations on the Clinical Use of Intravenous Sodium Azide**

*Jerry E. Schmitthenner and Joseph H. Hafkenschiel, Philadelphia, Pa.*

Seven severely hypertensive patients were each given an initial intravenous dose of sodium azide followed by a continuous infusion to keep pressure at normal levels. Observations were made on blood pressure, pulse rate, respiratory rate and symptoms for periods of 1 to 4 hours. Two of the patients were studied repeatedly with ECGs and ballistocardiograms (Starr table) during the observation period.

The initial dosage varied from 0.2 to 4.0 μg. per Kg. per minute, (average 1.6 μg.). Maintenance dosage varied from 0.25 to 1.14 μg. per Kg. per minute (average 0.41). Six patients showed a rapid fall in blood pressure, averaging 75 mm. Hg systolic and 33 mm. Hg diastolic. The remaining patient showed a fall from 220/130 to 190/120, slow in onset, in spite of a moderately high dosage in the range reported. Symptoms noted during the infusion were headache in three patients and faintness in one. Symptoms were usually relieved by breathing 100 per cent oxygen. None were considered severe. Pulse rate response showed marked variation from patient to patient. Blood pressure tended to be lower sitting or in 60 degree head-up position. Ballistocardiographic and ECG waves were more normal in one subject and unchanged in the other studied.

The most useful aspect of the sodium azide infusion appears to be the ready dissipation of the depressor effect when the dosage is reduced. There is a rapid return of a hypotensive effect when the infusion rate is increased. Since the authors were unable to control blood pressure levels in patients in hypertensive crisis, using other depressors such as protoveratrine without some untoward symptoms occurring, the effectiveness of sodium azide in this dosage range in lowering blood pressure with minimal unpleasant side effects is noteworthy. Our

study suggests that it may be useful in the short-term treatment of the severely hypertensive with encephalopathy or toxemia of pregnancy.

**Studies on the Circulation of a Permeable Substance (Thiocyanate) in the Human Forearm**

*Harold W. Schnaper and Edward D. Freis, Washington, D. C.*

Previous studies in this laboratory provided methods for studying the transcapillary exchange of permeable substances in local vascular areas. A mixture of impermeable T-1824 and permeable thiocyanate was injected into the brachial artery and multiple collections taken from an antecubital vein for 25 minutes. Since the volume of the forearm is small in relation to the total body, by using appropriate amounts of injectate, insignificant concentrations appeared in the general circulation. Thus, the complete washout of these substances was determined without contamination from recirculation.

In normal subjects the maximum loss of thiocyanate averaged 60 per cent as found previously. The percentage loss decreased to 30 per cent with markedly increased velocity of blood flow (local hyperemia). It did not increase above normal, however, with retarded flow (venous congestion or congestive heart failure). Normal rates of blood flow, therefore, appeared to provide the conditions for most efficient transcapillary exchange.

The equilibrium time for thiocyanate (point where net return began to exceed net loss) averaged 2.4 (S.D. 0.8) times the mean circulation time of T-1824. This constant relation was maintained despite a wide range of T-1824 mean circulation times varying from 13 to 310 seconds (local hyperemia, normals, venous congestion and congestive failures).

The relationship between the velocity of the intravascular and extravascular substances again was shown by the washout (virtual disappearance) times. In the normals, these averaged 7 minutes for T-1824 and 14 for thiocyanate; in local hyperemia, 1 minute for T-1824 and 2 for thiocyanate; in venous congestion, 15 minutes for T-1824 and 24 for thiocyanate and in congestive failure, 19 minutes for T-1824 and 26 for thiocyanate.

**Inactivation of Pherentasin by Antihypertensive Drugs**

*Henry A. Schroeder and H. Mitchell Perry, Jr., St. Louis, Mo.*

Pherentasin, a long acting vasoconstrictor procured from hypertensive arterial blood, was partly purified and assayed on a spirally cut rabbit aortic strip suspended in oxygenated Ringer's solution. Active material from 17.54 L. blood was compared with inactive from 16.8 L. and from 16.0 L. venous normotensive blood. The material appeared to act directly upon arterial smooth muscle, producing a slowly developing, sustained contraction. Inactivation studies revealed no antagonism by adrenolytic, cholinergic or sympatholytic agents. Six metal binding or chelating agents, of which 4 are used to treat hypertension (azide, nitroprusside, thiocyanate, hydralazine), inactivated the constrictor action. Comparative studies revealed that no simple primary vasoactive amines accounted for activity. Papain (but not 7 other proteolytic enzymes) and monamine oxidase caused inactivation, as did manganous ion but not 7 other trace metals. Drying, alkali, nitrous acid and ninhydrin all caused inactivation. There were dissimilarities in action and inactivation with angiotonin and Pitressin.

In 14 of 28 hypertensive patients, a similar constrictor was demonstrated in venous blood. After treatment with hydralazine in 4 positive cases, no constrictor material was demonstrated. From these studies it appears that the constrictor material contains an aliphatic peptide linkage, an unidentified trace metal, necessary for activity, primary amine and sulfur. Hydralazine is an agent which seems to inactivate it in vitro and in vivo.

**Phonocardiographic Study of Mitral Valvular Disease Complicated by Atrial Fibrillation. An Analysis of the Factors Responsible for Variations in the Time of the First Heart Sound and the Opening Snap**

*Mortimer L. Schwartz, Pierre R. Moret, Sidney R. Arbeit, Harold W. Grossman and Maurice N. Re, Jersey City, N. J.*

Two significant phonocardiographic findings have been described in patients with atrial fibrillation complicating mitral stenosis: (1) The duration of the "first time interval" (measured from the R wave of the ECG to the beginning of the first heart sound) varies inversely with the length of the preceding diastole and (2) the duration of the "second time interval" (measured from the onset of the second heart sound to the opening snap) is directly proportional to the length of the preceding diastole. It has been reported that neither of these variations appear if the additional lesions of severe aortic and/or mitral insufficiency are present.

Study of 6 patients with pure mitral stenosis and of 11 patients with mitral stenosis and a significant degree of regurgitation (all with atrial fibrillation) indicated that in any given patient the amount of variation in the "first time interval" closely approximated the amount of variation in the "second time interval."

While our findings generally confirmed the relationship of the time intervals to the preceding diastole, important exceptions were noted. In 3 cases of pure mitral stenosis, confirmed at operation, very little variation in these time intervals occurred.

In associated mitral insufficiency there were 3 instances of marked variations in these time intervals. Explanations in the literature for variations in the two time intervals are discussed. Our unexpected findings are thought to be due to an additional factor, the degree of flexibility of the mitral valve.

**A Clinical Study of One Hundred Cases of Severe Aortic Insufficiency**

*Jack Segal, W. Proctor Harvey and Charles Hufnagel, Washington, D. C.*

One hundred cases of severe aortic insufficiency are evaluated with emphasis on those clinical features which influence case selection for surgical intervention. Eighty-three patients were rheumatic, 12 syphilitic, 4 congenital and 1 traumatic. The average age was 34, and males predominated three to one.

The progression of symptoms in the syphilitic group was more than twice as rapid as in the rheumatic. The average rheumatic patient had rheumatic fever at the age of 13, developed hemodynamically significant aortic insufficiency at 20, and was asymptomatic until the age of 30. The symptomatic period ranged from 2 months to 30 years, averaging 6.4 years. The average syphilitic had the primary lesion at 20, developed significant aortic insufficiency at 36, and first experienced symptoms at the age of 43.

Palpitation and dyspnea were the earliest and most frequent symptoms in all etiologic groups. Angina occurred in almost 50 per cent of the rheumatic group. Bacterial endocarditis occurred in 22 per cent of the rheumatic group and was frequently followed by progressive cardiac decompensation. Hemoptysis only occurred with associated mitral stenosis.

Radiologic findings were left ventricular enlargement, aortic "jump" and rocking motion of the heart. Posterior displacement of the esophagus occurred in approximately 50 per cent of the patients and 60 per cent of these demonstrated expansion of the left atrium. ECG studies demonstrated normal sinus rhythm, left ventricular hypertrophy and frequently first degree A-V block. Atrial fibrillation, vertical electric axis and large P waves often indicated associated mitral stenosis.

Some patients were maintained for years on conservative medical management but, usually, progressive congestive failure occurred. A poor prognosis was associated with bacterial endocarditis, the coexistence of angina and congestive failure, syphilitic etiology, marked cardiomegaly, ventricular irritability and increasing age and duration of symptoms. The prognosis is especially grave following sudden onset of aortic incompetence, related to ruptured or inverted aortic cusps.

**Anatomic Location of the Electric Heart Center in Patients**

*George E. Seiden, Philadelphia, Pa.*

In the past, leads to measure dipole components were based upon representation of the body as a sphere with centric dipole. The inadequacy of this schema is revealed when parameters of torso shape and dipole location are considered, as demonstrated by Burger and van Milaan, Schmitt and Frank. Knowledge of dipole location, an extremely critical parameter, enables construction of orthogonal leads. Therefore anatomic location of the equivalent dipole in cardiac patients was undertaken.

The Frank data-fitting cancellation method was used. For each patient, cancellation data obtained from each of several four-electrode positions on the transverse plane were compared with similarly obtained data from a homogeneous torso-model in which anatomic location of the current dipole could be varied. When the dipole in the model is placed in an anatomic position, equivalent to that of the patient, matching of human and model data occurs, establishing the dipole location in the subject independent of the dipole moment. Movement of the model dipole one or two centimeters away from the determined location in each case results in non-correlation of human and model data.

The dipole location determined for each of 40 cardiac patients was compared with the location of the center of ventricular mass determined by orthodiagraphy. Ninety per cent of dipole locations clustered in a 5 by 5 cm. area forward and to the left in the transverse plane. Correlation between electric heart-center location and fluoroscopic center of ventricular mass was only approximate.

Accurate construction of orthogonal leads may be accomplished if the electric center is known for each individual. This determination is impractical for general clinical use. Lead systems, relatively insensitive, to variation in dipole location are being developed here and elsewhere. This study of the distribution of heart centers in patients defines the design requirements for such systems.

**The Effect of Digoxin Upon the Resting Circulatory Dynamics of Patients with Latent Cardiac Failure**

*Arthur Selzer, Carl L. Ebnother, Arthur O. Stone and Herbert W. Bradley, San Francisco, Calif.*

The conventional treatment of cardiac failure consists of 2 forms of therapy used in combination, use of (1) the cardiotonic effect of a digitalis-type preparation and (2) use of rest, Na restriction and diuretics. Each of these 2 methods alone is capable of controlling some patients adequately. The purpose of this study is to determine whether a beneficial effect of digitalis can be demonstrated in patients who appear to have been rendered asympto-

matic by rest, sodium restriction and diuretic therapy.

Ten patients were observed and treated until symptoms of cardiac failure disappeared and the dry weight was reached. Then a circulatory study was performed by means of cardiac catheterization during which a full dose of digoxin was administered. Circulatory measurements were performed during a half-hour control period and then repeated 25 and 50 minutes after the administration of digoxin. During the pre-digoxin period of the study, abnormally low cardiac indices were found in 6 of the 10 patients; all right atrial pressures were recorded as less than 10 mm. Hg. After digoxin 3 patients showed a significant fall in right atrial pressure and in 2 patients the cardiac index increased significantly. However, the mean change in right atrial pressure, the arteriovenous oxygen difference and the cardiac index was not considered significant. There was a significant slowing of the cardiac rate. As a result, the mean increase in stroke volume was 22 per cent.

It is concluded that in patients whose cardiac failure appears to be controlled by rest, Na restriction and diuretics, the resting cardiac dynamics, even though partially abnormal, are not consistently and significantly improved by administration of the full therapeutic dose of digoxin.

**The Effect of Exercise upon the Oxygen Removal Ratio in Patients with Mitral Stenosis**

*Arthur Selzer, Carl L. Ebnother, Arthur O. Stone and Thomas V. Feichtmeir, San Francisco, Calif.*

The normal increase in respiratory efficiency during exercise, evidenced by a higher extraction of oxygen from the inspired air, was shown by some investigators not to be present in patients with mitral stenosis. It was suggested that the reason for this alteration is the limitation of pulmonary blood flow, whereby the cardiac output fails to increase with exercise.

Cardiopulmonary function studies were performed in 34 patients with mitral stenosis. The change in oxygen removal ratio with exercise was correlated with the pulmonary arterial pressure, the pulmonary "wedge" pressure and the change in cardiac output. It is shown that in milder cases (class I and II) the oxygen removal ratio increases with exercise in a manner similar to that of normal individuals (mean change = 16 per cent increase). This increase was not observed in cases of severe mitral stenosis (class III and IV), where the mean change was a 2 per cent decrease. This failure to increase the respiratory efficiency with exercise could be correlated with the severity of dynamic alterations due to mitral stenosis as expressed by the mean pulmonary arterial pressure and the pulmonary "wedge" pressure. However, such a relationship could not be demonstrated between it and the changes in pulmonary flow induced by exercise.

It is concluded that the inability to elevate the oxygen removal ratio with exercise can only be shown in advanced cases of mitral stenosis and appears to be related to the severity of the disease. However, it bears no relationship and presumably is not due to the ability or the failure of the pulmonary blood flow to rise during exercise.

**Exercise Oxygen Consumption in Rheumatic Heart Disease**

*John T. Sharp, Ivan L. Bunnell and David C. Greene, Buffalo, N. Y.*

The standard 30-step, one-minute exercise test of Cournand is an accepted procedure in the clinical evaluation of patients with chronic pulmonary disease. In such patients one seldom sees reduction of the oxygen consumption during standard exercise, except in the presence of arterial hypoxemia, this reduction being due predominantly to ventilatory and diffusion defects.

Rheumatic mitral valvular disease is characterized hemodynamically by a subnormal pulmonary blood flow which is relatively fixed with respect to its response to exercise. In patients with mitral valvular disease, the opportunity arises of studying the dependence of the oxygen consumption during standard exercise upon pulmonary blood flow.

Thirty-five patients with rheumatic mitral valvular disease were studied; 20 had pure mitral stenosis, 7 had mitral stenosis and insufficiency and 8 had various associated valvular lesions. The mitral valvular lesion was usually considered the most significant from a hemodynamic point of view. Most patients underwent right heart catheterization by the usual technic on the day following the standard exercise test.

The oxygen consumption during the standard exercise test was below the lower range of normal in half of the patients studied and was below the mean normal value in all patients. A direct correlation was found between exercise oxygen consumption and pulmonary blood flow. An inverse correlation was observed between the oxygen consumption during standard exercise and mean pulmonary artery pressure, mean wedge pressure, total pulmonary circuit resistance and pulmonary vascular resistance.

**The Mode of Action of Certain Ionic Anticoagulants**

*Erwin Sheppard and Irving S. Wright, New York, N. Y.*

It has been reported that heparin acts on the blood coagulation mechanism as an inhibitor of thromboplastin generation, prothrombin conversion

d as an anti-Factor V and antithrombin. The atement that heparin per se, in the absence of its ofactor, would not block the conversion of fibrinogen has appeared in the literature many times. owever, early work in our laboratory has demonrated that heparin and other ionic anticoagulants ill increase the electronegativity of the fibrinogen olecule's surface. It was of interest to see if this crease in electric charge was sufficient in magnitude interfere with the conversion of purified fibrinogen. Light scattering studies were done to follow he polymerization of fibrinogen in the presence of brinogen as a function of ionic strength, concenration and pH. It has been demonstrated that eparin can block or retard the rate and degree of brinogen conversion in vitro due to repulsive orces. However, in vivo its anticoagulant activity is due to the formation of a potent antithrombin, arising from the heparin-cofactor complex.

Using heparin as the prototype, a variety of similar polyanionic compounds has been studied. As predicted, these compounds exhibit anticoagulant properties and their in vivo and in vitro activity is due to electrostatic repulsion, since agents comparable to heparin's cofactor have not been demonstrated. The results of these studies are summarized.

**A Successful Method for Artificial Maintenance of Cardiopulmonary Function**

*Norman E. Shumway, Marvin L. Gliedman, Donald W. Hannon, Charles E. Turbak and F. John Lewis, Minneapolis, Minn.*

An oxygenator of the gas dispersion type has been studied extensively in the laboratory and is ready for clinical application.

Near-physiologic flow rates, all-plastic construction of the extracorporeal unit and simplicity of technic are important factors in the consecutive survival of dogs undergoing 20 minutes of complete heart-lung by-pass and right ventriculotomy. Gravity drainage of blood from the vena cava to the oxygenator permits flow rates which comply with the physiologic demands of the animal. Oxygenated blood is maintained at a relatively constant level in a reservoir by regulating the speed of a simple finger pump used to propel blood into the arterial system. The animal determines his own flow rate. In general, flow rates have been much greater than azygous flows but definitely less than normal cardiac output. Flow rates of 1 L. per minute have been readily accommodated. Removal of all glass from the pump-oxygenator converted almost uniform failure to regular survival by eliminating fatal post-perfusion hemorrhage. Perfusion of the functionally isolated heart with blood from a glass oxygenator is enough to transmit a hemorrhagic diathesis to the animal even when little or no perfusate enters the circulation. Finally, simplicity of technic is important since only 500 cc. of blood is in the oxygenator circuit at any given moment; blood passes through the finger pump only once during each extracorporeal revolution; heat loss is minimized by concentric position of the oxygenator and the reservoir. The use of a combination filter chamber and bubble trap prevents any possible entrance of minute bubbles or fibrinous particles into the return flow.

**Current Indications for the Use of Anticoagulant Drugs in Cerebrovascular Disease**

*Robert G. Siekert and Clark H. Millikan, Rochester, Minn.*

The treatment of cerebrovascular disorders with anticoagulant drugs has been little explored. There are several varieties of cerebrovascular disease where this treatment appears to be of value. Thus far, anticoagulant therapy has been sharply limited to certain types of cerebrovascular disease. Certain features of the natural history and pathology, which suggested the potential usefulness of anticoagulant therapy in these specific disorders, are described.

The present tentative indications for anticoagulant therapy are intermittent insufficiency or thrombosis within the field of the basilar arterial system, intermittent insufficiency or occlusion of the internal carotid artery, multiple cerebral infarctions and prevention of thromboembolic phenomena in patients with rheumatic heart disease or mitral stenosis (Wright and McDevitt). A group of patients in each category, except the last one, has been observed and treated. The results of treatment are contrasted, in certain instances, with the natural history of the corresponding type of disorder. The patients treated with anticoagulants have had surprising amelioration of intermittent symptoms, presumed prevention or improvement of neurologic deficits and there has been an unexpectedly low mortality rate.

**A Study of the Parentage in Mongolism with Congenital Heart Disease**

*Jacob J. Silverman, Harold B. Berman and Henry Szancer, Staten Island, N. Y.*

Persons affected with mongolism afford a good opportunity for the study of congenital anomalies. Approximately 1 out of every 4 cases of mongolism suffers from a congenital cardiac defect. The purpose of the present study is to assess the paternal background of cardiac anomalies in mongolism.

One-hundred unselected cases, at postmortem examination in a State institution, form the basis of this study. There were 28 who demonstrated gross congenital cardiac defects. An interatrial septal defect was the most common anomaly (14, or 50 per cent); there were 6 with an interventricular septal defect, 4 with pulmonary stenosis and 3 with a

persistent atrioventricularis communis defect. One was unclassified.

The percentage of this group of 28 with cardiac anomalies was compared with the remaining 72 without cardiac anomalies. The age of parents, order of births, previous health of the mother and father, especially the history of viral infections, number of miscarriages and abortions and other factors were compared. No significant difference was noted in the two groups. In this study no special environmental factor affords a clue to the genesis of congenital heart disease in mongolism.

**Cardiovascular Disease and Abnormal Tryptophan Metabolism Associated with Malignant Carcinoid**

*Albert Sjoerdsma, Thomas W. Mattingly and Sidney Udenfriend, Bethesda, Md.*

A syndrome chiefly manifest by diarrhea, cutaneous flushes and cyanosis, and valvular heart disease has recently been described in association with malignant carcinoid (argentaffinoma). The discovery of large amounts of a potent pharmacologic agent, 5-OH-tryptamine or serotonin in carcinoid tumors and in the blood of patients with this syndrome, suggests that the syndrome may be related to overproduction of serotonin by the tumor.

Four patients with this condition were extensively studied, each exhibiting diarrhea, cutaneous vasomotor phenomena, and cardiac murmurs. Pulmonic stenosis and tricuspid incompetency were demonstrated in 2 cases by cardiac catheterization. Using methods developed in our laboratory, serotonin and its metabolic product, 5-hydroxyindole acetic acid (5-HIAA), were measured in the blood and urine of normals and patients with the carcinoid syndrome. Carcinoid patients showed hyperserotonemia and a greatly elevated urinary excretion of 5-HIAA. Measurement of urinary 5-HIAA serves as a simple diagnostic test for the condition. The role of tryptophan as a precursor of serotonin and 5-HIAA in man was established by tracing the fate of $C^{14}$ labelled tryptophan administered to carcinoid patients. Using balance technics, the production of 5-hydroxyindoles by the tumor was shown to vary in proportion to the dietary intake of tryptophan. The predominant route of tryptophan metabolism in the carcinoid syndrome is through the 5-hydroxyindole pathway.

Carcinoid patients may prove to be ideal subjects for studying the biochemistry and physiology of serotonin. It is likely that the overproduction of serotonin with concomitant deficiency of other tryptophan metabolites results in the lesions of the pulmonic and tricuspid valves. One should consider the carcinoid syndrome in patients with right sided valvular disease accompanied by unusual cutaneous flushes.

**Development of Hypertension and Cardiovascular-Renal Lesions During Adrenal Regeneration in the Rat**

*Floyd R. Skelton, Augusta, Ga.*

Twenty-four female weanlings, unilaterally nephrectomized, Sprague-Dawley rats were maintained on laboratory chow and 1 per cent saline. One half served as controls, while right adrenalectomy and left adrenal-enucleation were performed on the other half. Body weight, saline consumption and blood pressure were followed weekly. Half the rats in each group were sacrificed at 7 and 14 weeks respectively. Serum electrolytes were determined, organs were weighed fresh, fixed and examined microscopically.

At no time did the saline consumption or serum electrolytes of the adrenal-enucleated rats significantly differ from the control values. Despite this, the systolic blood pressure of the adrenal-enucleated rats, killed after 7 weeks, was 217 $\pm$ 9 mm. Hg, and in those killed after 14 weeks, it was 197 $\pm$ 16 mm. Hg, compared to the control values of 151 $\pm$ 6 mm. Hg and 145 $\pm$ 7 mm. Hg, respectively. The adrenal-enucleated rats developed renal, cardiac and cerebral enlargement and thymic atrophy at 7 weeks and the adrenals had regenerated to the same relative weight as both adrenals of the controls. In the adrenal-enucleated rats, killed after 14 weeks, renal and cardiac hypertrophy were also present, although less marked; but cerebral enlargement and thymic atrophy were not observed. The regenerated adrenals were significantly smaller than both adrenals in the controls.

In the enucleated rats, killed after 7 weeks, fibrinoid vascular necrosis in the kidney, heart, adrenals, pancreas, mesentery and ovaries was found. The brain was edematous and cystic with focal hemorrhages and neuronic degeneration. After 14 weeks, the lesions were less severe and less extensive than at 7 weeks. No cerebral lesions were present. The adrenals at both time intervals were somewhat depleted of lipoid and showed focal areas with intracytoplasmic colloid globules.

It is concluded that adrenocortical hyperfunction accompanies adrenal regeneration and, in suitably sensitized rats, has as its natural consequence the production of hypertension and cardiovascular-renal lesions.

**Physiologic Significance of Details in Very Low Frequency Ballistocardiograms**

*DeWitt Hendee Smith, Louis Fishman, Frank Shoemaker and Barton W. Knapp, Princeton, N. J.*

Usual direct or movable table ballistocardiographic records are so distorted by the effects of the restoring forces, present in the springs, that only the first events of each heart beat are legibly represented in the trace. Using a balsa wood platform

weighing six and one-half pounds, suspended as described by Yandell Henderson in 1905 so that the natural frequency is about a tenth of 1 c.p.s. and sensing acceleration, the authors obtain nearly undistorted BCG records with considerable detail. These are similar to, but more detailed and informative, than very low frequency records obtained by others. Characteristic features include individual widths of various excursions; I is narrow and deep, J is wide, nearly straight sided and notched, K is shallow but generally below the base line. Soon after K, there is a striking sharp deflection, usually downward, that appears to relate to the closure of the semilunar valves. Wider and slower upward deflections that follow are perhaps related to diastolic filling and/or other diastolic events. Notches near H may relate to mitral closure. Features in the HI downstroke relate to asynchrony of ejection from the right and left heart and have clinical importance. Numerous other notches and features, not seen in usual records, are present. Some of these are still to be related to physiologic events.

**The Carotid Artery Pulse in Aortic Stenosis**

*J. E. Smith, I. Hsu, Ludwig G. Lederer and J. M. Evans, Washington, D. C.*

The present study was undertaken to evaluate an indirect recording of the carotid pulse as an aid in the clinical diagnosis of aortic stenosis.

The carotid pulse tracing was obtained using a metal cup mounted on a wooden, halter-type, adjustable neckpiece. This permits the cup to be secured snugly over the carotid artery. The cup is connected through rubber tubing to a crystal-type pickup which produces an electric signal proportional to the pressure changes within the system. The tubing is four feet long and has a resonant frequency of 70 to 80 cycles, which produces marked amplification of the systolic vibrations of aortic stenosis. Carotid pulse tracings were obtained in 180 normal subjects, 84 patients with nonvalvular heart disease and 55 patients with valvular heart disease other than aortic stenosis. None of these cases showed systolic vibrations as found in aortic stenosis.

There were 33 individuals with aortic stenosis. In 12 fluoroscopy showed aortic leaflet calcification. This, in the absence of postmortem confirmation, was considered diagnostic. Of the 12, their ages ranging between 38 and 76 years, 10 showed carotid pulse of aortic stenosis. This is characterized by systolic vibrations superimposed upon a plateau-type contour with prolongation of the rapid ejection phase. The 2 subjects who did not show these findings were over 70 years of age and 1 was in congestive failure. Twenty-one patients, most of whom had rheumatic heart disease, clinically fulfilling criteria for aortic stenosis without fluoroscopically demonstrable leaflet calcification, showed the carotid pulse of aortic stenosis.

Three patients with mitral disease by clinical examination, also had the carotid pulse tracing of aortic stenosis.

**The Effect of Acute and Chronic Administration of Pentolinium Tartrate on the Blood Pressure and Cardiac Output in Hypertensive Patients**

*Josef R. Smith, Alberto Agrest and S. W. Hoobler, Ann Arbor, Mich.*

To determine how much the decline in peripheral resistance and the reduction of cardiac output affect the reduction of blood pressure achieved by pentolinium bitartrate, we measured the hemodynamic response to this drug in the sitting posture, both after acute subcutaneous and chronic oral administration. Cardiac output was measured by the Hamilton-Stewart principle, using radioiodinated human serum albumin as the tracer substance. This technic permitted multiple successive determinations on the same subject. The average value of the cardiac index in paired determinations in the control (seated position) was 2.84 l per $m^2$ per minute with an average deviation from the mean of 2.8 per cent and never exceeds 6.8 per cent.

In the acute studies on 5 patients, the mean blood pressure fell 36.7 per cent, the cardiac index 36.4 per cent and the cardio-pulmonary blood volume decreased 19.6 per cent. Changes in individual cardiac index determinations after drug injection paralleled blood pressure reductions with remarkable consistency, indicating that the blood pressure decline was largely the result of a decrease in cardiac output. In the chronic studies, after 6 to 128 days in 6 patients, these same indices remained depressed in every instance. The relation between the pretreatment and post treatment values averaged −24.1 per cent for the mean blood pressure, −25.9 per cent for the cardiac index. Plasma volumes were unchanged. In one case, maintained on ganglionic blocking agents for more than 2 years, the rise in blood pressure following discontinuance of treatment resulted in hemodynamic changes in the opposite direction.

These data indicate that orthostatic blood pressure reduction with a ganglionic blocking agent such as pentolinium bitartrate is accomplished largely by a reduction in cardiac output and not by a decline in peripheral vascular resistance and that over a reasonable period of time no compensatory mechanism is activated.

**The Diagnosis of Mitral Regurgitation by Cardioangiography**

*Philip W. Smith, Hugh A. Cregg and Karl P. Klassen, Marion, O.*

The difficulties inherent in the diagnosis of mitral regurgitation are well known. The quantitative

estimation of the amount of regurgitation is even more difficult. A method which provides accurate evaluation of the competence of the mitral valve would be of definite value to the internist and, particularly, to the surgeon. Clinical and radiographic evaluation, as well as catheterization studies to determine the degree of mitral regurgitation, have shown poor correlation with the actual findings at operation.

Percutaneous subxyphoid puncture of the left ventricle and direct injection of a 70 per cent diodrast has provided a simple and reliable method of detecting the presence and degree of mitral regurgitation. In cases having cardioangiography with subsequent mitral exploration, there has been close correlation between operative findings and the degree of regurgitation demonstrated by this method.

**Ebstein's Disease: A Typical Clinical Picture**

*Sidney S. Sobin and John L. Johnson, Los Angeles, Calif.*

Ebstein's Disease, or displacement of the origin of a leaflet of the tricuspid valve into the right ventricle, has only rarely been suspected ante mortem. Its literature has principally been concerned with anatomic data and in only a very few patients has the diagnosis been confirmed during life. Our experience with 6 patients has shown a typical pattern of the clinical, radiologic and heart catheterization data. These individuals are approximately normal in size, are either acyanotic or just slightly cyanotic, with slight to moderate incapacity, cardiac enlargement, variable systolic and mid-diastolic murmurs over the midsternum and apex and a constant but unusual ECG pattern of right bundle branch block. The roentgen findings are characteristic, the heart is moderately enlarged with an unusual configuration and undulation movements of the left heart border, the lung fields are normal or under-vascularized. Right heart catheterization demonstrates the tricuspid valve far to the left and above its usual position, with a demonstrably diminutive right ventricular chamber. The right heart pressures are normal or only slightly increased and an atrial septal defect can be shown by catheter passage or from right heart blood oxygen data. Angiocardiography may show the characteristic anatomic defects.

The diagnosis of Ebstein's Disease should be considered in an individual with congenital heart disease without or with minimal cyanosis, bizarre murmurs, atypical right bundle branch block, and a characteristic roentgen appearance of heart and lungs. It can be confirmed by catheterization and angiocardiography.

**The Angiocardiogram in Mitral Stenosis in Variable Clinical States Before and After Mitral Valvotomy**

*Louis A. Soloff, Jacob Zatuchni and Eugene V. Kelly, Philadelphia, Pa.*

This report is concerned with intracardiac flow in mitral stenosis as visualized by rapid simultaneous biplane stereoscopic angiocardiography, timed by the carotid pulse. Findings in 22 individuals without surgery and 31 with surgery are used.

Intracardiac circulation time did not exceed 6.3 seconds in the normal. With heart disease, it may be prolonged but did not exceed 9.1 seconds in absence of puddling, marked cardiomegaly or failure. In the normal, right heart, pulmonary and left atrial artery, circulation times are approximately equal and do not exceed intracardiac time. In mitral stenosis, there is disproportionate prolongation of pulmonary artery and left atrial times. Left atrial time exceeds pulmonary artery time, which in the absence of right heart failure, exceeds right heart time. Left atrial volume is 2 to 12 times that found in the normal. Increase in volume is not related to age or to known duration of rheumatic state. No relationship could be found between left atrial time and volume, or between opacification of left atrium and ventricle, to differentiate pure stenosis from stenosis with regurgitation or to predict the degree of stenosis.

The angiocardiographic pattern of mitral stenosis is not specific. It may occur also in stenosis with regurgitation, predominant regurgitation, and even in non-valvular heart disease. For equal sized hearts, circulation times tend to be longer with atrial fibrillation than with sinus rhythm. Those with failure are longer and even those without clinically apparent failure may develop shortened circulation times after intensification of a medical regimen. The overall pattern, however, is not changed by medical therapy and remains characteristic for mitral stenosis after mitral valvotomy. There are no angiocardiographic features that can differentiate those with and without surgery.

It is concluded that constant medication and static disability are necessary before changes in intracardiac flow can be attributed to mitral valvotomy. Changes or lack of changes in intracardiac flow with preservation of the pattern can be correlated with changes in size of and with pressure within structures, proximal to the mitral valve. This may form a basis of objective evaluation of mitral valvotomy.

**Diagnosis and Treatment of Patent Ductus Arteriosus with Pulmonary Hypertension**

*F. Mason Sones, Jr., Cleveland, O.*

Although a patent ductus arteriosus is usually recognized by the typical "continuous" or "machin-

er" murmur, patients having a large ductus, complicated by severe pulmonary hypertension, characteristically do not present the typical murmur. These individuals, who are actually the most severely disabled by the lesion, are frequently denied surgical cure because of errors in diagnosis.

Twenty-one patients, from 3 months to 45 years old, were studied during the past 5 years. In none was the typical murmur recognized. Non-specific murmurs, cardiac enlargement and manifestations of pulmonary hypertension were evident in each but exact diagnosis, particularly, differentiation from patients with large septal defects, was not possible on the basis of clinical findings. In twenty, diagnosis was established by cardiac catheterization with passage of the catheter through the ductus. Eight patients were infants in the first year of life. Fifteen were younger than 5 years, and 6 were adults. The utilization of effective catheterization technics for application to small infants are discussed. Operation was not advised in 2 adults with predominant right-to-left shunts because of apparently irreversible pulmonary vascular disease. In the remaining adults and all of the children, large vessels were divided. There were 2 operative fatalities.

Controlled arterial hypotension was employed during surgery in adults with advanced degenerative changes and aneurysmal dilatation of the aorta and pulmonary artery. The technic of this procedure is described. It is simple and safe in application and greatly reduces the hazard of uncontrolled hemorrhage.

**Clinical Methods for Estimating the Work of the Heart**

*Isaac Starr, S. I. Askovitz, W. Feder and A. Schild, Philadelphia, Pa.*

In experiments in which "systole" was simulated at necropsy, the following curves were recorded; "cardiac" ejection at each instant of "systole," blood pressure at the root of the aorta, blood pressure in the femoral artery and the ballistocardiogram (BCG). From the first two, work can be estimated by mathematic integration multiplying the flow at every instant by the pressure at that instant. This is a method that is far more accurate than any which can be applied to living men or mammals. The result of these estimates, which may be called true work, has been taken as a target. By mathematic means, we sought the best method of estimating it from peripheral blood pressure and the BCG, and from peripheral blood pressure alone.

Therefore, in estimating the heart's work, we developed several methods which could be used by doctors, working in the clinic. A method, based on the BCG, the peripheral blood pressure and the subjects' age, yields a correlation with true work of 0.88 and its standard deviation is 23 per cent of the mean value for left ventricular work of healthy young adults. Using the femoral blood pressure alone, the correlation of the best clinical estimate of work with true work is 0.91 and the standard deviation 21 per cent of the healthy-young-adult mean value. This latter method can be adopted for use with blood pressures secured by the auscultatory method. After this has been done, the method can be applied to Hunter's data on the average blood pressure of Americans at different decades of life.

These results clearly show, despite the well known increase of average blood pressure as age advances, that the work of the left ventricle decreases steadily until, at 60 years of age, it is about two-thirds of the value found at 20 years of age.

**Clinical Use of Purified Streptokinase-Streptodornase (Varidase) Preparation in the Lysis of Intravascular "Clots"**

*Mario Stefanini, Boston, Mass.*

We have previously reported on the partial purification of Streptokinase-Streptodornase (Varidase) preparations and the physiologic effects of the intravenous administration of this material on the hemostatic mechanism in normals and our preliminary results on the therapeutic effectiveness of these products in various thromboembolic conditions. Use of two consecutive injections of purified "Varidase", 1,000 units per Kg. weight per hour over 4 hours, with an intervening period of 6 hours has become our standard procedure, following comparison of many different technics.

Patients, studied thus far, include 74 cases divided as follows: (1) acute thrombophlebitis, 71; (2) mesenteric thrombosis, 2 and (3) thrombosis of right central retinal vein, 1. Typical changes of the hemostatic mechanism were induced in 72 of these cases. Therapeutic results were favorable. In acute thrombophlebitis, there was prompt decrease of pain, edema and inflammation, all of which disappeared within 48 to 72 hours. This pattern was seen in 65 of 71 cases. Two patients developed pulmonary infarction 3 and 5 hours, respectively, after administration of purified Varidase, perhaps a hazard in this type of treatment.

The mechanism of the therapeutic effect of Varidase in acute thrombophlebitis is not clear. Work on the effects of Varidase in experimental thrombosis in animals may not be entirely comparable to findings in man, since much higher doses than in man are needed to activate the fibrinolytic mechanism in animals. It is likely, however, that these enzymes act by favoring dissolution of intravascular thrombi, thereby producing a reduction of symptoms, notably inflammation.

**Thrombophlebitis—a Manifestation of Systemic Disease**

*Irwin D. Stein and Alice Macauley, Mt. Vernon, N. Y.*

Thrombophlebitis of the peripheral veins is all too frequently considered an entity in itself. This may be misleading if causes such as pregnancy, trauma or varicose veins have been excluded. Frequently, thrombophlebitis appears as an early manifestation of an underlying systemic disease. In migrating or recurrent superficial phlebitis, such an association is now generally accepted as being pathognomonic of visceral malignancy, usually of the tail of the pancreas. This concept has been helpful in establishing the diagnosis of the underlying disease.

Since 1952, we have followed 52 patients in whom local causes for phlebitis were excluded. In 34 patients, a more basic and serious disease process was found. In 26 of these patients, a variety of neoplastic processes were found and proven by laboratory examination, x-ray films and biopsy and subsequently by necropsy. Some of the other underlying disease processes were: polycythemia vera, gout, thromboangiitis obliterans and cirrhosis of the liver.

Malignancies of the gastrointestinal tract appeared most frequently in this series, and there were only 2 instances of carcinoma of the tail of the pancreas. We think that an attack of phlebitis should be considered as a possible clue to an underlying disease process and that the patient should be studied thoroughly to rule out this possibility.

**Detection of Coronary Insufficiency by the Ergonovine Stress Test-Studies in Man and Animals**

*Isadore Stein, Joseph Weinstein and Seymour H. Rinzler, New York, N. Y.*

Ergonovine maleate, 0.1 to 0.4 mg., was administered intravenously as a test for coronary insufficiency in 149 patients with effort angina but a normal resting ECG. It was given similarly to 114 controls (normal subjects and patients with chest pains other than angina). The test was negative in all of the latter group. In the patients with effort angina the ergonovine test was positive in 122 (81 per cent), as shown by prompt appearance of chest pain and/or ECG changes (depression of S-T segment and/or inversion of the T wave). In 112 of the patients with a positive test, both ECG changes and chest pain occurred together, 6 had chest pain alone and 4 had ECG changes without pain. Changes in the blood pressure and pulse rate after ergonovine were minimal.

Ergonovine-induced pain could be prevented, reduced or relieved by brief application of a rapidly cooling volatile spray (ethyl chloride or halohydrocarbon mixture) to reference zones of cardiac pain or, less consistently, by similar application to remote areas. Spraying, however, did not prevent ECG changes characteristic of coronary insufficiency. Ergonovine, plus spray with a volatile coolant, offers a useful test for coronary insufficiency which is (1) relatively pain free; (2) does not cause tachycardia which may confuse the ECG interpretation; (3) it can be done on patients who for other than cardiac reasons cannot exercise and (4) the ECG changes may be quickly reversed to normal by nitroglycerin.

Ergonovine tests were similarly carried out on rabbits maintained on stock and cholesterol diets. Rabbits, on stock diets for 11 weeks or less, gave negative responses to ergonovine, while rabbits maintained on the cholesterol diet for 20 to 22 weeks all showed positive responses (significant depression of the S-T segment, following ergonovine). At the postmortem examination, controls, as well as animals kept on the cholesterol diet for the shorter period, had no atheromatous involvement of the coronary arteries. On the other hand, all rabbits with positive tests showed advanced occlusive disease of these vessels with areas of myocardial damage.

**Production of Hyperlipemia and Early Atherosclerosis in Rabbits by a High Vegetable Fat Diet**

*Alfred Steiner, New York, N. Y.*

Attempts to produce an elevation in serum lipids and resulting atherosclerosis by dietary means have been unsuccessful without the feeding of large amounts of cholesterol or cholesterol rich foods. In this study, high vegetable fat diets, free of animal sterol, containing 30 to 40 per cent fat were fed to 43 rabbits for periods of 5 to 12 months. The source of the vegetable fat was ground peanuts.

This resulted in an increase in serum cholesterol, serum phospholipid, total serum lipid and C to P ratio; and an increase in the $\beta$ lipoprotein fraction of the serum, as determined by paper electrophoresis. On microscopic examination of the ascending and thoracic aorta, lipid deposits in the intima and underlying media were present in 10 of 33 rabbits at the end of 5 to 12 months. Small areas of gross aortic atherosclerosis developed in the aorta in 2 rabbits.

**Immunologic Evidence of Group A Streptococcal Infection in Patients Undergoing Mitral Commissurotomy**

*G. H. Stollerman, W. F. Lynch, M. A. Dolan, D. Young and J. B. Schwedel, Irvington-on-Hudson, N. Y.*

Fifty-three patients, undergoing mitral commissurotomy for mitral stenosis, were studied to determine whether the antecedent group A streptococci infection was related to the histologic findings in the biopsied atrial appendage and the postop-

erative development of clinical manifestations, suggesting reactivation of rheumatic fever.

Serial determinations of the serum titers of antistreptolysin O, antihyaluronidase and antistreptokinase were made preoperatively and each month during a postoperative period of at least 3 months. Throat cultures were made at monthly intervals in most cases and, whenever possible, prophylaxis against intercurrent streptococcal infection was maintained.

Forty-three of the 53 patients studied were found to have low serum levels (below 200 units per cc.) of all 3 antibodies, immediately prior to surgery. In these patients recent preoperative streptococcal infection was not apparent. Six were found to have characteristic Aschoff nodules in the biopsied auricular myocardium. In an additional 6 patients the histologic findings were suggestive of rheumatic myocarditis. There were 10 patients in whom immunologic evidence of recent streptococcal infection was found preoperatively. Of these, 2 had typical Aschoff nodules in the biopsied atrial appendage and two had lesions, suggesting rheumatic myocarditis. Nine patients developed manifestations suggestive of the "postcommissurotomy syndrome." Of these, 2 patients showed no immunologic evidence of streptococcal infection pre- or postoperatively. Of the remainder, 3 patients had immunologic evidence of recent streptococcal infection preoperatively and the 4 others showed a significant antibody rise during the postoperative period, prior to the onset of the postcommissurotomy syndrome.

The data indicate that Aschoff nodules may often persist in the myocardium without immunologic evidence of recent streptococcal infection by the methods employed. It also appears, however, that streptococcal infection is relatively common postoperatively (it occurred in 14 of 53 patients) and should be considered among the factors influencing the patient's postoperative course, particularly the reactivation of rheumatic fever.

**The Electrocardiogram and Hypopotassemia**

*Borys Surawicz, Harold A. Braun, William B. Crum, Robert L. Kemp, Seymour Wagner and Samuel Bellet, Philadelphia, Pa.*

Fifty patients with hypopotassemia were studied to establish the frequency of various clinical manifestations attributed to hypopotassemia, the correlation of these manifestations with the severity of hypopotassemia and the manner in which the clinical manifestations of hypopotassemia are affected by abnormal concentrations of other electrolytes. This report deals only with the correlation between the ECG and the plasma potassium.

Patients were divided into 3 groups: group A consisted of 20 patients with plasma potassium of 3.0 to 3.48 mEq. per liter, group B of 13 patients with plasma potassium of 2.7 to 3.0 mEq. per liter, and group C of 17 patients with plasma potassium 2.0 to 2.7 mEq. per liter. One limb lead, usually II, and one precordial lead, usually $V_3$, were analyzed in each case. An ECG pattern was considered *typical* of hypopotassemia if all of the following signs were present in one of the two examined leads: (1) a U wave amplitude exceeding 0.1 mv.; (2) U wave amplitude greater than T wave amplitude in the same lead and (3) S-T depression greater than 0.5 mm. The pattern was also considered typical if 2 of these signs were present in one lead and at least one sign in another of the examined leads. An ECG pattern was considered *compatible* with hypopotassemia if two of the signs were present in one lead, one sign in each lead, or one of the first two signs in one lead.

In group C 83 per cent of the patients had typical and 6 per cent had compatible patterns. In group B 31 per cent had typical and 45 per cent had compatible patterns and in group A 10 per cent had typical and 45 per cent had compatible patterns. The ECG was better correlated with plasma potassium level than any clinical sign or symptom. U-wave amplitude was proportional to degree of hypopotassemia, but was also increased by bradycardia. Abnormal plasma pH did not preclude typical ECG features of hypopotassemia.

**Creatine Content of Biopsied Human and Rabbit Heart Muscle**

*Don C. Sutton, George C. Sutton and Egbert H. Fell, Chicago, Ill.*

In previous reports, we have established the normal levels of creatine in whole blood and skeletal muscle and also the changes occurring during heart failure, using Folin and Wu's picric acid method as modified for the photelometer by Hoffman. Normal blood values agreed with those found by Beard; approximately 3 mg. per cent. We established normal skeletal muscle creatine levels at approximately 350 mg. per cent.

Cardiac surgery offers the possibility of obtaining biopsies from the heart. The creatine level in sections from 39 atrial appendages averaged approximately 448 mg. per cent.

One patient, from whom an atrial appendage biopsy had been taken, died on the table. In this case the atrial appendage contained 570 mg. per cent creatine. The patient expired 15 minutes later. An immediate biopsy of ventricular muscle contained 290 mg. per cent of creatine. Similar values were found in rabbit hearts before and after death.

Alpha-tocopherol appeared to prevent the fall of creatine values in heart muscle, immediately after death. We believe this to be the first report of the levels of creatine in nearly normal heart muscle.

### Electrocardiographic Observations during Quinidine Administration to Patients with Atrial Fibrillation

*George C. Sutton, William P. Swisher and Don C. Sutton, Chicago, Ill.*

Quinidine sulfate was given orally 125 times to 92 patients with chronic atrial fibrillation, in an attempt to convert the abnormal rhythm to sinus rhythm. Eighty attempts were successful, while 45 attempts failed. This represents a conversion rate of 64 per cent.

Among the 80 instances of conversion 23 (28.8 per cent) progressed through a stage of atrial flutter. The study should be divided into 2 periods. ECGs and 18 successful conversions were obtained during the earlier period; only 2 instances, in both daily ECGs were recorded, demonstrated a transient stage of atrial flutter, as atrial fibrillation was converted under the influence of quinidine to normal sinus rhythm. In the later part of our study, which contained 62 successful conversions, daily ECGs were recorded and 21 progressed through a stage of atrial flutter before sinus rhythm was restored. Eighteen relapses occurred while the patient was still under observation, and 13 again progressed through a stage of atrial flutter with increasing atrial rates, as the levels of plasma quinidine declined until the rhythm was finally atrial fibrillation. Among the 45 cases of failures, 24 (53.3 per cent) were changed into atrial flutter with the atrial rates generally fluctuating in inverse ratio to the plasma levels of quinidine. All but 1 case went back to atrial fibrillation, as soon as the plasma levels of quinidine showed appreciable decline.

The frequency, with which atrial flutter is noted in cases of atrial fibrillation which are treated with quinidine for conversion to sinus rhythm, probably depends on the diligence of the investigator and the frequency with which ECG studies are performed, as the quinidine level in blood rises and the conversion time approaches. Our observation would tend to support the unitary nature of atrial fibrillation and flutter, in which the only difference is the rate of discharge of the ectopic focus. Quinidine decreases the rate of discharge from the ectopic focus.

### The Diagnosis of Anomalous Pulmonary Venous Connection at Cardiac Catheterization

*H. J. C. Swan, Howard B. Burchell and Earl H. Wood, Rochester, Minn.*

During the past 2 years, 25 cases have been studied in which one or more of the pulmonary veins was connected to the right atrium or to a tributary thereof. Five cases were examples of total anomalous connection; in one case the veins from the left lung and in 19 cases the right pulmonary veins connected anomalously. In only 1 patient was the atrial septum intact.

*Partial Anomalous Connection.* The diagnosis is established in the case of an extracardiac communication by the precise localization of an extracardiac site of arterialization, utilizing a direct-reading cuvette oximeter. The lung, or part of the lung from which the anomalous connection originates, can be identified (1) by manipulating the catheter into the anomalously connected vein and (2) by means of indicator-dilution curves recorded following injection of dye into the right or left pulmonary artery or a branch thereof. The latter method applies, whether the anomalous connection is extracardiac or is directly to the right atrium. The characteristics of dilution curves, recorded following injection into the artery supplying a lung which drains anomalously are (1) an appearance time which is longer than that for the indicator injected at an upstream site (for example, the vena cava) and (2) a contour, similar to that obtained when an indicator is injected at the site of the anomalous connection.

*Total Anomalous Connection.* The diagnosis is made in this instance on (1) the demonstration of identical values for the oxygen saturation of blood, drawn from the pulmonary trunk or right ventricle and simultaneously from a systemic artery and (2) the close similarity between the contour of dilution curves, recorded following injection in the pulmonary arteries or right ventricle and in the vena cava with a shorter appearance time for the caval sites.

### Clinical Studies with SKF-54451 (Miopressin)

*Francisco Tangco, Walter Redisch, Lothar Wertheimer, Charlotte Rappaport and J. Murray Steele, New York, N. Y.*

Clinical responses to a combination of Dibenzyline, Protoveratrine and Rauwolfia in varying doses have been observed over an 18-month period in 20 patients whose systolic and diastolic arterial pressures had been consistently above normal levels. Eight patients were hospitalized, 8 were on home care program and 4 were ambulatory. The ward patients had been hospitalized for long periods of time with consistently elevated systolic and diastolic pressures, taken irregularly during that time. When daily blood pressure readings were done by the same person, a considerable drop was observed. This is distinguished from the commonly observed drop following hospitalization. On administration of the drugs, 6 of the 8 hospitalized patients, 2 of 8 home-care patients and 3 of the 4 ambulatory patients, had a decrease of 15 mm. Hg or more in diastolic and 30 mm. Hg or more in systolic pressure. Most patients developed postural hypotension at some time during the study.

Symptoms were present in 10 patients; 7 reported relief while on drugs. Moderate lowering of heart

rate occurred in most patients on administration of the combined drugs at certain dosage levels, with no further change on increase in dose. Stuffiness of the nose, drowsiness and sleepiness were the most frequent side effects.

It was necessary in each patient to ascertain the optimal dosage level, above which no further drop in pressure occurred, but side effects increased.

Decrease in heart size was reported radiologically in one case. Renal function, ECG tracings and hemograms were not altered. Eye-ground findings improved in one case, progressed in another and remained unchanged in 18. The reported observations indicate that the level of arterial pressure can be controlled with the mixture of drugs studied, in a considerable percentage of patients with long-standing hypertension.

**Various Effects of Smoking on the Ballisto-cardiogram**

*O. Tannenbaum, H. Vesell and J. Schack, New York, N. Y.*

Effects of smoking on the BCG were investigated by means of a BCG, recording the body movements in three planes simultaneously, with an ECG as timing reference. It was a modified Dock type BCG, yielding a "diagnostic" trace. The instrument was standardized simultaneously in each direction of motion by means of an eccentric rotating disc, driven by a constant speed motor at 5 c.p.s. and the sensitivity of each galvanometer adjusted so that the amplitude of each sine wave was equal.

There were 100 subjects in this study, 82 were normal according to customary clinical examinations including ECG findings and fluoroscopy. Based on similar examinations were 18 subjects with coronary artery disease. Ages ranged from 18 to 76 years. The BCGs were recorded before, immediately after and 5 minutes after smoking. The test was only performed after a lapse of 1 hour after the last cigarette was smoked. A standard brand of cigarette was employed.

In the normal subjects under 40 years of age, 15 per cent had abnormal responses in the H-F BCG after smoking. These consisted of changes in amplitude, deterioration of wave form, and respiratory variation. In the group over 40 years of age, the percentage of abnormal responses increased to 25 per cent. However, in many of those subjects where the amplitude of the waves diminished in the H-F BCG, there was a compensatory increase in the amplitude in the A-P plane. The latter individuals all had vertical or semi-vertical hearts.

There were 18 subjects with ischemic heart disease of whom 15 had an abnormal control BCG. The 3 individuals with normal or borderline BCG findings had deterioration of wave form after smoking. Four of the subjects with coronary artery disease whose control BCGs were abnormal, tended to normalize after smoking. Thus changes in cardiac position may be responsible for some of the changes of the BCG, attributed to smoking.

**Sensitivity of the Respiratory Center in Patients with Cor Pulmonale**

*Alberto C. Taquini, Aquiles Roncoroni, Pedro Aramendia and Antonio Ross, Buenos Aires, Argentina*

Varying degrees of anoxemia, hypercapnia and an increase in blood bicarbonate concentrations are frequent findings in patients with cor pulmonale, depending on the type and severity of the underlying pulmonary pathology.

Increase in arterial $CO_2$ tension was found in these patients in direct relation to the decrease in effective alveolar ventilation. Notwithstanding the augmented $pCO_2$, the pulmonary ventilation remained normal or even below normal. These findings could be explained by decrease in the sensitivity of the respiratory center to $CO_2$. Different aspects of this problem were studied and form the basis of this presentation.

Pure oxygen breathing resulted in decreased ventilation, probably through suppression of the anoxic drive and in spite of an increased arterial $CO_2$ tension. Breathing 5 per cent $CO_2$ in oxygen was capable of suppressing anoxemia without a decrease in ventilation. Breathing 5 per cent $CO_2$ in air-produced hyperventilation with a moderate decrease in anoxemia. The level of ventilation obtained under this condition was lower than that expected in comparison with normal subjects.

A carbonic anhydrase inhibitor (acetazoleamide), which decreases blood bicarbonate was used to see if a decrease in blood bicarbonate would bring about a change in the sensitivity of the respiratory center to $CO_2$. In normal subjects, blood bicarbonate and $CO_2$ were diminished without definite changes in the respiratory response to breathing $CO_2$.

Patients with cor pulmonale showed a marked decrease in blood bicarbonate with augmented alveolar ventilation and a subsequent decrease in the arterial $CO_2$ tension; the ventilatory response to $CO_2$ inhalation under these conditions was higher than previously. These facts are interpreted as showing that chronic increases in blood bicarbonate concentration and its relation to the $pCO_2$ frequently have a greater effect than $CO_2$ narcosis in the respiratory depression observed in chronic cor pulmonale.

**The Value of the Measurement of the QTc in the Prognosis of Rheumatic Heart Disease in Children**

*Leo M. Taran and Nelly Szilagyi, Roslyn, N. Y.*

A group of patients who died during the course of acute rheumatic heart disease were studied. The

purpose of this study was to observe in detail the events preceding death. The common denominator of all cases was the existence of acute carditis over a long period prior to complete cardiac deterioration. With the exception of a few patients, all had congestive failure immediately preceding death; all had some form of endocarditis; all showed obvious cardiac enlargement; and many developed a crude arrhythmia preceding death. It was the intention to sift out the most important factor related to the death of the patient. The disturbed hemodynamics, resulting from anatomic changes in the cardiac structures, were not found to be the dominant factors in the downward progress. The presence and severity of the acute myocardial involvement expressed in the form of carditis was the decisive feature in all cases. The diagnosis of carditis in all cases was clear cut, but the severity of the carditis was not always easily assessed.

The best index for measurement of the severity of carditis was found to be the QTc. All of these cases had moderate to marked prolongation of the QTc for variable periods of time preceding death. The degree of cardiac insufficiency and the rapidity of complete cardiac deterioration was almost directly proportional to the extent of the prolongation of the QTc. This group of patients seemed to fall into three categories: (1) those who had a moderately prolonged QTc (0.440 to 0.450) and were definitely in an earlier phase of cardiac failure; (2) those who had a marked prolongation of the QTc (0.450 to 0.460) and were either in actual or imminent failure; (3) those who had a severe prolongation of the QTc (0.460 to 0.487); and were in overt failure, which resisted management. The extent of anatomic cardiac deformity was about the same in the three groups. The degree of acute myocardial disturbance seems to be the dominant factor in the immediate and eventual prognosis and this factor may be assessed from the prolongation of the QTc.

**Congenital Aortic Stenosis: Early Clinical Manifestations and the Late Development of the Classical Syndrome**

*Helen B. Taussig and Jesse Schessel, Baltimore, Md.*

Aortic stenosis is the counterpart on the left side of the heart of pulmonary stenosis on the right side. In both, the obstruction may increase as the patient grows. Either one may lead to great cardiac enlargement and cardiac failure. Obviously, accurate diagnosis is the essential prerequisite for treatment.

Recent experience in the Harriet Lane Home Cardiac Clinic has shown that the clinical findings in mild sub-aortic and aortic stenosis may closely resemble those of a septal defect. Two of our patients were originally diagnosed as having atrial septal defects because of a systolic murmur over the pulmonic area, a tendency to a right axis deviation and a hilar dance; another was diagnosed as a ventricular septal defect because the murmur and thrill were maximal close to the left sternal border in the third and fourth left interspace, but cardiac catheterization showed no evidence of any shunt. In each instance it was only as the patient grew and the obstruction increased in severity that the clinical picture changed and the patient finally developed classical signs of aortic stenosis; i.e., a basal systolic murmur and thrill to the right of the sternum, transmitted to the vessels of the neck, a narrow pulse pressure and ECG evidence of left ventricular strain.

These observations indicate that the so-called "classical" findings of aortic stenosis are late clinical manifestations of congenital aortic stenosis. Furthermore, the early signs of congenital aortic stenosis are totally different from the early signs of rheumatic aortic stenosis.

Surgical correction of aortic and sub-aortic stenosis is more difficult than that of pulmonary stenosis, in part because of the necessity of entering the left ventricle and, in part because of great variation in the pathology. The stenosis may be valvular or there may be a membraneous subaortic shelf of tissue or there may be a muscular ridge of tissue beneath the aortic valve. In 1 patient, the aorta at its base was abnormally small. Nevertheless, it is reasonable to hope that with improvement in surgical technic, the malformation, at least in some instances, will be amenable to surgery. Until that time comes the finding of classical signs of aortic stenosis is a strong indication for restriction of activity.

**A Method for Inducing Thrombi of Desired Length in the Ear Veins of Rabbits. The Effect of Dicumarol and Tromexan on Recanalization of Thrombosed Veins**

*Alexander Taylor, Edgar V. Allen and Hiram E. Essex, Rochester, Minn.*

An ear of each rabbit was shaved and a portion of the peripheral ear vein of desired length (2.5 cm.) was isolated by means of black silk ligatures which were prevented from cutting into the vein by placing under them, on both sides of the ear, parallel to the vein, short pieces of small caliber polyethylene tubing. A minute quantity of a thrombin solution (1000 units thrombin per 1 ml. saline) was then injected through a No. 25 needle into the isolated venous segment. Coagulation occurred rapidly. To prevent the escape of thrombin into the general circulation through anastomotic channels, a large sheathed curved clamp was applied to the ear for a few minutes in such a way as to completely surround the isolated venous segment. Approximately 24 hours later, the ligatures were removed and an intravenous clot of desired standard length, adherent to the vessel wall remained.

The intravenous thrombus was proved to be of standard length, and to completely occlude the vein, by introducing a radiopaque fluid (diodrast 35 per cent) into the peripheral ear vein of the anesthetized rabbit, distal to the thrombus and making a roentgenogram as the fluid was being injected. Small metal V-shaped arterial clips were used to indicate what were considered to be the site and length of the thrombus. A photographic technic, using transillumination, was employed which confirmed the location and length of the thrombus. Using 18 rabbits, which were fed a standard diet, the time required for recanalization of the vein was found to average 15 days. It was demonstrated that the administration of dicumarol and tromexan increased the speed with which recanalization of the veins occurred.

**Observations on Pulmonary Embolism in Chronic Congestive Heart Failure**

*William R. Tench, Clearwater, Fla.*

Pulmonary embolism in non-cardiac disease is inferred by well known criteria. Pulmonary embolism is well established as a complication in half of the patients dying in congestive heart disease, but clinically, it is usually ascribed to some other facet of heart disease, producing attacks of anginal pain, dyspnea, pneumonia and arrhythmia. It was observed, that in such patients, mercurials became increasingly ineffective, tachycardia often developed and the arrhythmias were those principally of digitalis intoxication.

A study was then made of hospital records and autopsy protocols of patients who died of chronic congestive heart failure between January 1946 to July 1954, chiefly at the Peter Bent Brigham Hospital, Boston. Fifty showed pulmonary embolization, 50 did not (controls). They were quite evenly divided between coronary and rheumatic heart disease. No recent myocardial infarction was included. Suitable criteria were established to determine the presence of edema refractory to mercurials, tachycardia and digitalis toxicity.

Thirty-five patients in the pulmonary embolism group were given mercurials and of these, 32 were refractory. Of 38 such patients in the control group, 10 were refractory. The combination of digitalis intoxication, plus tachycardia was found to have occurred in 26 patients in the embolism group and in 7 of the controls. The occurrence of a triad consisting of mercurial-fast edema, digitalis intoxication and tachycardia, was found to be almost invariably associated with multiple pulmonary embolization. This triad was found in 20 of the embolism group, and in only 2 of the controls. A satisfactory diuresis is of some assurance that pulmonary embolization is not present.

When a cardiac patient develops a clinical state suggestive of the criteria so well established for noncardiac pulmonary embolization, the additional finding of tachycardia, digitalis toxicity and/or edema refractory to mercurials is good evidence that this complication of chronic congestive heart failure is present.

**Comparison of the Clinical Results in Transventricular and Transaortic Commissurotomy for Rheumatic Aortic Stenosis**

*Joseph F. Uricchio, Robert Litwak and Charles P. Bailey, Philadelphia, Pa.*

The first surgical method to correct the commissural fusion of rheumatic aortic stenosis, transventricular commissurotomy, requires an entrance into the left ventricular cavity through its muscular wall for the passage of a dilating instrument which engages the valve from below. Recently, transaortic commissurotomy has been developed and the valve may be reached safely through the aorta itself.

This review compares the mortality, postoperative complications and subsequent clinical course of 65 patients with aortic stenosis, isolated or coexisting with adynamic aortic insufficiency, operated on by the transventricular route and 40 patients with identical lesions operated on by the transaortic technic.

The mortality of transventricular commissurotomy was 18.4 per cent. The cause of death in most instances was ventricular fibrillation. Postoperative cardiac complications without mortality occurred in 19.3 per cent and included atrial fibrillation, congestive heart failure and pericarditis. A follow-up evaluation, limited to patients at least 3 months after surgery, revealed 2 late deaths due to subacute bacterial endocarditis and heart failure. Significant improvement was reported in fatigue, dyspnea, angina, syncope and vertigo. Dynamic aortic insufficiency was produced in 7 per cent of the survivors.

The operative mortality in transaortic commissurotomy was 10 per cent. Cause of death was either fatal cardiac arrhythmia or hemorrhage. Cardiac complications without mortality occurred in 38.8 per cent of the patients. Six deaths occurred during the follow-up review, 3 as a result of staphylococcic subacute bacterial endocarditis. Dynamic aortic regurgitation did not occur in a single instance. A gradient across the aortic valve was reduced by transaortic commissurotomy in those cases on whom left heart catheterization was performed.

Transventricular aortic commissurotomy is a procedure which should be abandoned in favor of the transaortic technic. The former relies on a dilator that cannot be controlled at the site of its action, it causes a high initial mortality rate and is likely to produce dynamic aortic insufficiency.

**Experimental Hypertension Produced by Constriction of the Carotid Sinus Area in Dogs**

*G. E. Wakerlin and E. Crandall, Chicago, Ill.*

Bilateral constriction of the carotid sinus area by a plastic clamp with a two-thirds reduction of the volume pulse of the sinus and the internal and external carotid arteries, produced a significant, sustained increase in arterial blood pressure in 14 out of 15 dogs. Half of the dogs showed a gradual increase over 2 to 4 months, following constriction; the others showed a rapid increase during 1 to 3 weeks. Three dogs showed increased irritability and aggressiveness for 3 to 4 months following operation, but the pressure increase persisted after the nervous tension disappeared. Otherwise there were no gross clinical changes. Heart rates are normal. Urinalyses, appetites and body weights have remained normal during the 4 to 25 months of hypertension. Preliminary studies indicate intact vagus nerves. Passive immunization with antirenin to hog renin was without antihypertensive effect. Control dogs, subjected to bilateral implantation of the plastic clamps immediately lateral to the carotid sinus and untreated control dogs observed during the same 25 months, showed no significant change in their normotension. The pathogenesis of this experimental hypertension is under study. While altered carotid sinus function has not been ruled out, an alteration in cerebral hemodynamics seems more likely.

**Treatment of Spontaneous (Essential?) Hypertension in Dogs with Renin and Antirenin**

*G. E. Wakerlin, J. I. Katz and J. H. Skom, Chicago, Ill.*

Socalled spontaneous hypertension in dogs resembles early essential hypertension in man, and knowledge of the pathogenesis of the former may help elucidate the latter. Since passively transferred antirenin (hog) is antihypertensive in dogs with experimental renal hypertension, we decided to study the effect of hog renin and the passive transfer of antirenin in spontaneously hypertensive dogs.

Three spontaneously hypertensive dogs were treated with crude hog renin and six with semipurified hog renin from cortex in doses of 2.5 to 20 D.U. (dog units) per Kg. daily and intramuscularly for 4 to 19 months. These dogs showed highly significant antihypertensive effects which were correlated with the plasma antirenin titer. Similarly prepared control tissue extracts were without antihypertensive effects in 4 spontaneously hypertensive dogs. Five spontaneously hypertensive dogs were passively immunized on two separate occasions with high titer homologous antiserums, containing antirenin to semipurified hog renin. Significant antihypertensive effects were obtained. Control experiments with low titer antiserums were ineffective. The passively produced antirenin titers, not only correlated well with the antihypertensive effect but the effective titers were also similar to those produced by injections of semipurified hog renin into spontaneously hypertensive dogs. Control normotensive dogs, including two with high normotensions, showed no depressor effect from crude or semipurified hog renin with antirenin production or from passive immunization with antirenin. Necropsy showed normal kidneys and no other abnormalities in the spontaneously hypertensive dogs. Inasmuch as these results indicate that spontaneous hypertension in the dog is on a renal renin basis, they suggest further investigation of the possibility that essential hypertension in man may have a similar pathogenetic basis.

**Electrocardiographic and Hemodynamic Correlation in Atrial Septal Defect**

*Weldon J. Walker, Thomas W. Mattingly, Bryon E. Pollock, David B. Carmichael, Thomas W. Inmon and Ralph H. Forrester, Fort Sam Houston, Tex.*

The ECG findings of 91 patients with uncomplicated atrial septal defects have been analyzed. The diagnosis was confirmed and pressures and flows determined by cardiac catheterization in all cases. The diagnosis was substantiated at surgery or necropsy in 21 cases. Fourteen patients have had hemodynamic and ECG studies repeated following surgical closure of their defect. The QRS duration varied from .06 to .12 seconds but in only 14 patients was it greater than 0.10 seconds. The pattern of incomplete right bundle branch block was present in 65 per cent; 29.5 per cent showed right ventricular hypertrophy and 5.5 per cent had normal electrocardiograms. Hence, if one considers the diagnosis of atrial septal defect as untenable in the absence of right bundle branch block, one would incorrectly diagnose more than one-third of these patients. There was a progressive shift of the electric axis to the right corresponding to increasing pulmonary hypertension. The incidence of incomplete right bundle branch block decreased sharply as the pulmonary pressure increased without change in the average duration of the QRS complex. Following surgical closure there was a general reduction in resting right ventricular systolic pressure and a shift of the electric axis toward the left. The pattern of incomplete right bundle branch block has been observed to emerge from that of right ventricular hypertrophy after closure of the atrial defect. It is suggested that the characteristic RSR′ seen in lead $V_1$ represents an intermediate degree of right ventricular hypertrophy as modified by a change in the right ventricular size and position due to the altered hemodynamics in atrial septal defect. It is

further suggested that the RSR′ often represents the normal three main cardiac vectors of the heart rather than right bundle branch block.

### The Direct Surgical Repair of Congenital Intracardiac Defects

*H. E. Warden, M. Cohen, R. A. Dewall, R. C. Read, J. B. Aust, R. L. Varco and C. W. Lillehei, Minneapolis, Minn.*

To date 43 patients have undergone cardiotomies and repair of their congenital intracardiac defects under direct vision at normal body temperature by means of controlled cross circulation or by continuous arterial reservoir method of perfusion. This group has included the surgical correction of such anomalies as interventricular septal defects, tetralogy of Fallot and *atrioventricularis communis* with an overall survival rate of 63 per cent.

The controlled cross circulation method of perfusion utilizes a donor individual as an oxygenator and a mechanical pump as the heart, to maintain an adequate circulation through the patient during the period of total cardiac by-pass. The circulatory flow rate required has been based on the azygous or low flow principle (one-eighth to one-quarter of the basal cardiac output) and has been supplied by the simple pump which circulates equal amounts of oxygenated blood from the donor' artery to recipient's aorta and venous blood from the recipients caval system back to the donor's venous circulation. Then, with the patient supported in this fashion, his cardiac inflow may be totally occluded, the heart opened wide and an intracardiac procedure carried out.

The experience gained from the clinical application of cross circulation emphasized the fact that, especially in infants and small children, relatively small volumes of arterial blood were sufficient to support the patient during the period of perfusion. Hence the development of the reservoir method of perfusion which employs the mechanical principles of cross circulation, but substitutes reservoirs of arterial and venous blood for the donor individual in the operative procedure.

Blood for the arterial reservoir has been obtained from compatible blood bank donors whose arms have been heated to 45 C. for 15 minutes prior to collection. As much as 500 cc. of blood, possessing the chemical characteristics of arterial blood, may be obtained from a vein of such a preheated arm.

### An Electrocardiographic Pitfall—"The Juvenile Pattern"

*R. H. Wasserburger and T. H. Lorenz, Madison, Wis.*

Persistent RS-T segment and T wave abnormalities in the presence of normal QRS complexes have been observed in the unipolar precordial leads in apparently normal Negro and white adults. A large group of patients with these changes were studied in detail. Many had previously been diagnosed as having organic heart disease on the basis of ECG changes. Evidence is presented to show that these abnormalities are most often "functional" in origin.

These striking changes can be produced or exaggerated by brief hyperventilation and ameliorated or abolished by reassurance, alkalinizing potassium salts or vagal blocking agents. The role of emotional disturbances in the production of these changes is stressed.

In an extension of this study, 400 adults with normal routine ECGs were studied after a period of brief hyperventilation. Approximately 15 per cent of these patients showed similar RS-T segment and T wave patterns which superficially simulated myocardial ischemia. Since hyperventilation occurs with each of the various exercise tests, further doubt is added to the significance of these tests in assessing coronary circulation.

### The Supporting Role of Digitalis in the Treatment of Atrial Fibrillation with Quinidine

*Samuel A. Weisman, Los Angeles, Calif.*

Insufficient importance, perhaps, is attributed to the therapeutic value of digitalis in the treatment of atrial fibrillation with or without quinidine.

The purpose of this report is to discuss the pharmacologic properties of digitalis and quinidine based on experimental and clinical studies. Experiments carried out in dogs with the aid of ECG studies showed that the 2 drugs were not synergistic in their action on the heart. We have used these drugs in several hundred cases of atrial fibrillation with good results.

### Study of Variation in Blood Volume of Healthy Males Using Radiochromium

*R. Wennesland, J. Hopper, Jr., E. Brown, J. L. Hodges, Jr., O. Guttentag, I. N. Tucker and B. Bradley, San Francisco, Calif.*

Reliable standards for predicting normal blood volume are essential in order to make use of volume determinations in physiologic and clinical studies. A modification of the $Cr^{51}$ method of Sterling and Gray has been used to study the variability of red cells and whole blood volumes in 173 healthy males (prison inmates) in the third to fifth decade of life. Each subject was screened for general health and somatotyped by the method of Sheldon. Occupation and habits of physical activity were recorded.

Derived regression equations relating volumes to body measures are: (1) *volume of RBC (liters) = .0176 × weight (Kg.) + .766. (S.D. 0.219);* (2) *volume of RBC = .0287 × height (cm.) − 3.024.*

(*S.D. 0.221*); (3) *volume of RBC = .0115 × weight + .0183 × height − 2.02.* (*S.D. 0.195*); (4) *volume of whole blood = .0289 × weight + .0337 × height − 3.562.* (*S.D. 0.37*). The last 2 equations represent plane surfaces; no curvature could be detected by mathematic analysis of the data. The coefficient of variation for red cell volume is roughly 10 per cent and for whole blood volume, 8 per cent.

Tests have been made to determine whether the relationship of volume to body size is influenced by somatotype or habits of physical activity. Consideration of these factors fails to reduce the variability of the data.

Twenty-five subjects have been studied twice or more. The standard deviation of paired volume determinations was approximately 100 cc. of red cells. Analysis of details of the method shows that technical error is far less important than biologic factors in determining variance from mean values.

**Vectorcardiographic Patterns in Rheumatic Heart Disease: Results in Fifty-six Autopsied Cases**

*Gerald H. Whipple, Gabriel Cosio and Harold D. Levine, Boston, Mass.*

In a correlative study of 56 cases of significant rheumatic heart disease at autopsy, the clinical data and various observations and measurements made on the isolated heart were compared with the antemortem ECG and spatial vectorcardiograms. Certain distinctive vectorcardiographic patterns were noted to be associated with the dominance of a particular valvular deformity in a number of instances. For example, predominant mitral insufficiency tended to produce a QRS loop which was long and narrow without much forward or backward displacement of its apex as viewed in the horizontal plane. Dominant aortic stenosis tended to produce a similar long and narrow loop whose apex was disposed more posteriorly. Mitral stenosis usually produced a non-specific, right ventricular hypertrophy pattern. Occasionally, however, it was associated with a QRS loop which appeared relatively normal, the only distinguishing feature being a terminal appendage which was directed posteriorly and superiorly, differentiable from the similar appendage that may be found in some normals by the absence of slowing of the rate of inscription in that segment. The absence of these and other suggestive patterns did not mean that a typical mitral insufficiency or aortic stenosis, for example, did not exist. However, when a typical pattern occurred in a patient with known rheumatic heart disease, there appeared to be a good correlation between these empiric observations and the valvular deformities found at autopsy. The use of this information has been occasionally helpful in the evaluation of patients prior to cardiac surgery.

**Improved Method of Evaluating Circulatory Shunts by use of a Direct Recording Ear Oximeter**

*Curt A. Wiederhielm and Robert A. Bruce, Seattle, Wash.*

A new amplifying system for directer recording from an ear oximeter, with linear response to oxygen saturation or Evans blue concentrations, has permitted quantitative analysis of time and concentration relationships of dye dilution curves. Appearance time (A) and buildup time (B) are derived directly from the records. Extrapolating down-slope limb of curve by Hamilton's method (using semilogarithm paper) permitted replotting extrapolated portion on the original record. Disappearance time constant (D) was defined as duration for a one-third reduction in concentration on this exponential downslope curve. Following the technic of Broadbent and Wood, ratios of time values were used to evaluate shunts independently of cardiac index. Thus B/A and D/A were utilized to describe right to left, and left to right shunts, respectively. These ratios were not affected by low cardiac indices in absence of shunting, and permitted recognition of left to right or right to left, or mixed shunts in most instances. Furthermore, whenever ratios were within normal range (0.2 to 1.2 for B/A and 0.0 to 1.4 for D/A) major shunts were excluded and the curve could be utilized to calculate cardiac output. Minor L to R shunts and coronary circulation were still included in this value, however. It is concluded that direct recording of dye dilution curves are of value in checking patients with murmurs for possible shunts, as well as readily estimating the cardiac output in the absence of significant shunts.

**Effluographic Determination of Potassium Flux in Heart Muscle as Related in Time to Potential Changes (ECG) and Contraction Event**

*W. S. Wilde, J. M. O'Brien and I. Bay, New Orleans, La.*

A heart is intensely pre-enriched with potassium, $K^{42}$, by intraperitoneal injection. The coronary circulation of the excised heart is then cannulated and perfused with Ringer albumin so that the outflow is caught on a moving filter paper strip. Serially timed segments of the paper are cut onto counting planchets to measure the $K^{42}$ leached from the heart in rest and during systole. A constant foreign radioactivity is added to the perfusate ahead of time and as a second count represents volume of outflow collected on the paper strip. The ratio of the two isotopes, leached out $K^{42}$ and volume indicator, then yields the concentration of $K^{42}$ in the outflow. The record of $K^{42}$ concentration against time we call an "effluogram." We showed for the first time that the

potassium released during activity is a true pulse related to the T wave of the turtle heart. The method is a new concept in rapid-fire sampling of ultra-micro volumes. Volumes as small as 0.003 ml. collected every 0.06 sec. have been collected. There is no pipetting error, since no pipette is used. Volume sensitivity depends only upon the intensity of radioactivity one adds to the perfusate. A recent record shows 6 systoles recorded during 110 seconds and comprising 1200 samples. All 6 $K^{42}$ waves have a similar shape.

The $K^{42}$ release is scattered by the arborization of the coronary bed and it suffers a time delay because of coronary travel distance. We calibrate this by constructing an indicator dilution curve, such as is used for measuring cardiac output after a sudden large dose of indicator is injected. A model of a vascular bed in which colored strings are drawn through the several flow channels illustrates properties of the scattering phenomenon.

**Harmonic Analysis of Blood Pressure Values Obtained During Parabiotic Exclusion of the Heart**

*Robert Wilder, William M. Nelson, Samuel J. Megibow, George Robinson and Lester Blum, New York, N. Y.*

During exclusion of the heart by a cross-transfusion or parabiotic technic, it is desirable to approach normal blood pressure levels.

With this method, the entire venous return to the heart is drawn off through a catheter and pumped into a companion animal for oxygenation. It is then returned via the same electro-mechanical device to the arterial tree through the left subclavian artery. The pulsatile nature of this flow locks the aortic valves resulting in an empty heart.

Blood pressure recordings consistently exhibit a recurring pattern of harmonics with one or more fundamental frequencies present in the same wave form. An examination of these component wave forms is of particular interest as an expression of a systemic circulation, independent of the heart and maintained solely by the extracorporeal pump.

A graphic method of harmonic analysis and a practical application of Fourier's theorem, expressed as the sum of a number of sinusoidal variations in the study of these blood pressure wave forms, are presented. A periodic variation is exactly repetitive after successive intervals of time.

These wave forms are integral multiples of a fundamental frequency. Harmonics of two or more different fundamental frequencies may also occur. Amplitude, period, cycle, crest, trough and peaks are discussed in relation to the operative steps of the exclusion.

**Pulmonary Stenosis, Ventricular Septal Defect and Left-to-Right Shunt (Acyanotic Fallot's Tetralogy)**

*Paul Winchell, James Redington and Fouad Bashour, Minneapolis, Minn.*

In 5 adult patients, studied by cardiac catheterization, pulmonary stenosis, ventricular septal defect and predominant left-to-right shunt at the ventricular level were found. Arterial oxygen saturations were near normal, but marked desaturation was produced by exercise in one patient.

A sixth patient, aged 53, presented cyanosis, clubbing, polycythemia and the clinical findings of tetralogy of Fallot. The diagnosis was confirmed at catheterization but a large ventricular left-to-right shunt was also present.

Mild pulmonary stenosis in the presence of ventricular septal defect may prevent the development of pulmonary hypertension (Eisenmenger's complex), and not be severe enough to cause cyanosis. This may be one mechanism allowing prolonged survival in the rare case of tetralogy of Fallot reaching middle or advanced age.

This lesion is potentially completely correctable. Contemplated surgery should include relief of the pulmonary stenosis and closure of the ventricular septal defect since simple resection of the pulmonary stenosis may lead to even further increases in pulmonary blood flow, pulmonary hypertension, and cardiomegaly.

One diagnostic pitfall concerns the pressure gradient across a normal pulmonary valve in the face of left-to-right shunt. This may amount to as much as 40 mm. Hg, a point proved by studies of atrial septal defects, before and after surgical closure. This would seem to represent relative, or functional, pulmonary stenosis with an anatomically normal pulmonary valve.

**The Induced Digital Vasoconstrictive Reflexes in Health and Disease**

*Travis Winsor, Wilbur A. Selle and Youssef Mawardi, Los Angeles, Calif.*

The induced digital vasoconstrictive reflexes are involuntary reactions which follow stimulation of sensory organs or which may arise from other sources such as the cerebral cortex. This report deals with an analysis of these reactions which follow cortical and sensory stimulation.

Five hundred reflexes were studied among 110 subjects employing 8 different stimuli, (cerebration, inspiration, anticipation, cold, tickle, pain, a startling sound and a startling light). The reactions to sound took place an average of 3.2 seconds after stimulation and were complete, usually in 45 seconds. The total volume and volume pulsation of the digit decreased and was associated ordinarily with sweat

ing, as shown by simultaneously recorded psychogalvanograms. The reflex could not be inhibited voluntarily by mental effort but could be fatigued by repeated stimulation for 2 to 4 minutes. The magnitude of the reflex was related to the magnitude of the stimulus. The reflexes were abolished by lesions in the receptor organ, afferent pathways, or in the cerebrum and by novocaine injected into the spinal canal, sympathetic vertebral ganglia or peripheral nerves. Tetra-ethyl ammonium chloride, dimethyl di-ethyl piperidinium chloride, the hydrogenated alkaloids of ergot, and benzyl-imidazoline, parenterally, blocked these reflexes. The reflex pathway involved in the reaction was shown to be the receptor organ, afferent nerves to subcortical tissue (possibly the sympathetic vasomotor center) with efferent sympathetic fibers in the cord and peripheral nerves to the effector organ. Vasoconstrictions were produced by positive conditioning and these responses were blocked by negative conditioned reflexes. The magnitude of the reactions was related to the degree of arterial disease which was present.

The presence of a large reflex preoperatively was correlated with good results following lumbar sympathectomy in 20 cases. The presence of the reflex, before and its absence soon after lumbar sympathectomy, provided a means of determining the completeness of sympathectomy in 30 patients. Repeated determinations at intervals of months provided a means of determining the rate of return of sympathetic function after surgery. A return of function was observed in 1 of 30 patients in whom lumbar sympathectomies ($L_2$ and $L_3$) were performed. The simultaneous recording of this reflex from a digit on each extremity assisted in localizing lesions in the sympathetic nervous system in 12 patients.

**Significance of the Onset of Angina Pectoris as an Acute Episode in the Course of Coronary Artery Disease**

*Stanley J. Wittenberg, New York, N. Y.*

The lack of uniformity in the clinical description and the ECG changes in the group of syndromes, described as coronary failure, coronary insufficiency with or without occlusion and premonitory symptoms of acute myocardial infarction, lead the author to believe that they are simply gradations between transitory ischemia and acute myocardial infarction.

In an effort to clarify our clinical concepts of gradations of acute episodes in the course of coronary artery disease, the author has selected 10 patients who demonstrate minimal symptoms of gradual or sudden onset of angina pectoris. Their clinical course and serial ECG changes are presented and discussed. In 8 patients, there was a lag in ECG changes of several weeks to several months. These changes varied from T-wave changes alone to the classical serial changes of acute myocardial infarction. The significance of T-wave changes, following the onset of angina pectoris is discussed. One patient demonstrated transient ventricular tachycardia following an exercise tolerance test. The relationship of this finding to the occurrence of sudden death in patients with coronary artery disease is discussed.

The author believes that these patients suffered a gradual occlusion of a major coronary artery and concomitant development of collateral circulation to the affected area. The rate of occlusion exceeded the development of collateral supply, and necrosis of an area of myocardium resulted. The clinical expression of this process was the occurrence of angina pectoris.

**Peripheral Venoconstriction in Human Congestive Heart Failure**

*J. Edwin Wood and Julius Litter, Boston, Mass.*

The participation of the venous system in the syndrome of congestive failure is denoted by the frequent use of such paradoxic terms as venous distension and venoconstriction with reference to this state. The more exact term "venous distensibility" implies the measurement of venous distension under known amounts of "effective" (internal minus external) venous pressure. This method has been applied to patients, with and without congestive heart failure.

Prior to each experiment, the effective local venous pressure (internal minus external pressure) and the venous volume of the forearm segment in the plethysmograph were reduced to a low, constant and reproducible value. This was done by adjusting the water pressure on the forearm to a level which exceeded the previously determined, natural local venous pressure by an amount, sufficient to free the subsequent measurements from possible changes in systemic venous pressure. Local effective venous pressure was then increased by raising the pressure in a proximal congesting cuff by 30 mm. Hg. The resultant forearm volume increases if small, indicated peripheral venoconstriction and, if larger, indicated venodilatation.

Eighteen patients with congestive heart failure, associated with elevated systemic venous pressures, had a mean venous distensibility of 2.9 cc. per 100 cc. of tissue (S.D., 0.5 cc.). Twelve patients with congestive heart failure but normal venous pressures had a mean venous distensibility of 3.7 cc. per 100 cc. (S.D., 0.8 cc.). Ten patients with no cardiovascular disease had a mean venous distensibility of 4.5 cc. per 100 cc. (S.D., 0.5 cc.). Five patients with congestive heart failure were restudied after compensation occurred and venous distensibilities had increased from 2.3 to 3.5 cc., 3.2 to 4.3 cc., 2.1 to 4.4 cc., 2.5 to 3.3 cc. and 2.4 to 3.1 cc. per 100 cc.,

respectively. These studies indicated that peripheral vasoconstriction was present in the patients with congestive heart failure and that it tended to remit, as the patient improved.

**Influence of Thiopental Sodium Anesthesia and of Pentobarbital Sodium Anesthesia upon the Cardiac Output of the Dog**

*Robert A. Woodbury, Floyd Davis and Clinton B. Nash, Memphis Tenn.*

Though thiopental sodium and pentobarbital sodium are widely used for general anesthesia their influence upon the cardiac output has not been investigated until the last few years. Previous studies have shown quite diversified results, have generally included inadequate controls and have failed to follow the cardiac output in one individual for the full period of the anesthesia.

The influence of thiopental sodium and pentobarbital sodium were each studied in 10 male dogs which had been previously fasted and trained to lie quietly in a supine position on a padded dog board. Cardiac output determinations were accomplished by the pressure-pulse contour method of Hamilton and Remington. Prior to the administration of any drug the heart rate, mean blood pressure, respiratory rate, pressure pulses, circulatory time, blood volume and hematocrit were obtained. The animal was then anesthetized by slow injection of the barbiturate. The animal was maintained in a constant level of anesthesia as judged by pain reflexes (such as pinching of web of skin between the toes) and by the eyelid reflex, as well as the rate and depth and type of respiration for periods varying from 4 to 7 hours. In the case of thiopental sodium, cardiac output, heart rate and mean blood pressure were obtained at 15-minute intervals. In the case of pentobarbital sodium these determinations were obtained every thirty minutes.

Thiopental sodium anesthesia produced a progressive decrease in the cardiac output reaching a minimum after 2 hours of anesthesia. The value remained significantly low for the next 2 hours. Pentobarbital sodium produced a progressive decrease in cardiac output for the first 2 hours after which it remained relatively constant for about 2 hours and then returned toward the control value during the next 3 hours. There was no significant change in blood pressure despite the fact that the cardiac index had been reduced on the average by 35 to 40 per cent of the control values.

**Thrombophlebitis: A Possible Clue to Cryptic Malignancy**

*Kenneth R. Woolling and Richard M. Shick, Indianapolis, Ind.*

Thrombophlebitis occurred as the initial or principal presenting sign of unsuspected carcinoma in 15 cases. If primary and other secondary varieties of thrombophlebitis, distinct from the one under consideration, can be excluded, this type of thrombophlebitis may be a diagnostic clue leading to earlier recognition and treatment of previously unrecognized carcinoma. In this series, the proved primary sites of carcinoma were the pancreas in 3 cases, ovary in 3, stomach in 2, lung in 1, and breast in 1; in 1 case, the primary site probably was the prostate gland, and in 4 cases, the primary site was undetermined. A characteristic of this variety of thrombophlebitis is its relative refractoriness to anticoagulant therapy. The mechanism of development of this hypercoagulability of the blood is unknown.

**Indications for and the Results of Long Term Anticoagulant Therapy**

*Irving S. Wright, Ellen McDevitt and Willam T. Foley, New York, N. Y.*

A satisfactory method for the evaluation of long term anticoagulant therapy has been finally evolved. In this study, the patients served as their own controls. Their course has been studied for a period of months prior to being placed on anticoagulant therapy and during this time, a record of thromboembolism and other complications was carefully compiled. They were then placed on anticoagulant therapy and observed for long periods of time. A comparison was then made regarding the incidence of thromboembolic complications.

Since the course of most of the diseases under consideration tends to be progressively worse if they are not under effective therapy, the balance, if anything, is weighted against the therapy. Nevertheless, the results in the long term treatment of (1) rheumatic heart disease with artrial fibrillation and multiple embolization; (2) recurrent myocardial infarction; (3) cerebral thrombosis and embolization and (4) recurrent thrombophlebitis of various different basis have all shown very striking improvement in the prognosis, as a result of long term therapy.

**Relationship Between Central and Peripheral Arterial Pressure Pulses in Aortic Stenosis in Man**

*J. Leo Wright, Howard B. Burchell and Earl H. Wood, Rochester, Minn.*

Intra-arterial pressure pulses were recorded simultaneously from multiple sites in the arterial system in 10 patients with aortic stenosis and in 12 normal persons. Graduated withdrawals of Peterson-type arterial catheters through the aortic-brachial and the aortic-femoral arterial systems permitted study of alterations in pulse contour during peripheral transmission.

The following characteristics were noted: (1)

in aortic stenosis, there was relatively less transformation in contour, as the pulse was transmitted distally; (2) an anacrotic pause, which occurred near the systolic peak, was noted and it was usually more sharply demarcated centrally than peripherally; this pause appeared an average of 185 msec. (range: 166 to 207) after the onset of the pulse recorded centrally as compared to 132 msec. (112 to 166) at the radial pulse; (3) the systolic peak was late, averaging 254 msec. (237 to 297) after the onset of the pulse centrally (normals, 166, range 118 to 219) and 229 msec. (211 to 273) at the radial pulse (normals, 100, range 95 to 106); (4) there was a decrease in systolic pressure peripherally from an average of 119 mm. Hg (range, 100 to 142) for the central pulse to 116 mm. Hg (range, 94 to 133) at the radial area, while in normals, systolic pressures increased from 125 mm. Hg (range, 113 to 146) to 140 mm. Hg (range, 128 to 154), respectively; (5) the decrement in diastolic and mean pressures peripherally, which averaged 6 (4 to 8) per cent in patients with aortic stenosis, was not significantly different from normals.

### A Clinical Study of Complete Heart Block

*James C. Wright, M. R. Hejtmancik and George R. Herrmann, Galveston, Tex.*

Eighty-four cases of complete heart block, proven by the ECG, have been carefully studied and the data analyzed. Complete A-V heart block, meeting our criteria, is a relatively rare arrhythmia, occurring more commonly in males, with the peak incidence in the fifth to eighth decades of life.

A variety of causes were encountered, the most common being coronary atheromatosis, which was often a complication of hypertensive arteriolar disease. Digitalis intoxication was present in almost a third of the 30 cases in this series.

The associated clinical, radiologic and ECG abnormalities which were related to the underlying etiology were analyzed. ECGs taken before, during and after transient episodes of complete block were compared. It was found that previous bundle branch block was present in 80 per cent of our patients with complete A-V block. The width of the QRS was thus revealed as an unreliable criterion of the position of the idioventricular pacemaker. The higher the ventricular rate, the higher is the idioventricular focus in the conduction tissue regardless of the QRS interval. The arrhythmia was symptomatic of itself in approximately 50 per cent of the cases, with half this number showing actual Adams-Stokes episodes.

Drug therapy, specifically directed toward the arrhythmia and the prevention of symptoms, but excluding those of digitalis intoxication, was instituted in 40 per cent of cases and included the use of the sympathomimetic amines and digitalis. Of the former group, Isuprel appeared to be the most uniformly effective. Appropriate use of these various agents depends on the recognition of the underlying mechanism disorder producing symptoms. Quinidine and Pronestyl are dangerous, and should be avoided, even if there appear episodes of ventricular acceleration.

The prognosis in patients exhibiting complete heart block depends on the stability of the idioventricular pacemaker at a high level in the conduction tissues and the absence or presence of other mechanical disorders and associated cardiac defects. When symptoms appear, average life expectancy is generally 5 years or less, though notable exceptions occur. Prognosis was extremely grave in patients who suddenly and early edeveloped complete heart block after acute myocardial infarction.

### Clinical and Hemodynamic Studies of Tricuspid Stenosis

*Paul N. Yu, Dwight E. Harken, Frank W. Lovejoy, Jr., Robert E. Nye and Earle B. Mahoney, Rochester, N. Y.*

Five female patients with predominant rheumatic tricuspid stenosis were studied by cardiac catheterization. The diagnosis was made before catheterization in 4 cases and established in all by operation or autopsy. All had associated mitral stenosis. Clinical features included distended cervical veins; the characteristic rumbling diastolic murmur over the lower sternum, intensified by inspiration; absence of signs of marked pulmonary hypertension, even if the patient is greatly disabled; disproportionate right atrial enlargement by X-ray study, compared to limited right ventricular enlargement; and P pulmonale by electrocardiogram. Angiocardiography in one patient demonstrated prolonged retention of dye in a large right atrium.

Cardiac catheterization revealed a diastolic pressure gradient across the tricuspid valve, increased by exercise. The pulmonary artery and pulmonary artery wedge pressures were distinctly lower than in patients comparably disabled by predominant mitral stenosis. Combined mitral and tricuspid valvuloplasty performed in 4 patients resulted in symptomatic improvement. One operation employed a new combined approach through a left hemi-thoracic incision. One patient, operated on in two stages, had no improvement after adequate mitral valvuloplasty. Physical signs of tricuspid stenosis persisted. Tricuspid valvuloplasty then resulted in marked improvement, softening of the murmur and disappearance of the opening snap.

At operation, a decline in left atrial and pulmonary artery pressures followed mitral valvuloplasty and a fall in right atrial pressure followed tricuspid valvuloplasty. Postoperative catheterization in two patients revealed disappearance of the diastolic tricuspid pressure gradient. Pulmonary artery pressure had risen slightly in one patient whose

cardiac output increased and had not changed significantly in the other.

These patients represent about 5 per cent of all patients studied for mitral valve surgery. When mitral and tricuspid stenosis coexist both valves should be adequately fractured. Coexistent tricuspid stenosis should be excluded when adequate mitral valvuloplasty fails to produce the expected improvement.

**The Response to Acetylstrophanthidin**

*Jacob Zatuchni, Jairo Velasquez and Louis A. Soloff, Philadelphia, Pa.*

This report is concerned with the response to acetylstrophanthidin by normal and 28 individuals with varying structural and functional cardiac derangements, with and without previous digitalis and after digitalis loading.

No ECG or systemic effects were observed in the normal subjects after the use of 2.4 mg. of acetylstrophanthidin, which is twice the minimal digitalizing dose in individuals with static cardiac disability. Adequate digitalization is recognized either by adequate control of ventricular rate or appearance of signs of toxicity. Acetylstrophanthidin produced no change in the Q-T interval or ST-T portion of the electrocardiogram.

The digitalizing dose is much greater in those with acute heart failure. In those with associated illnesses precipitating cardiac failure, therapeutic effect may not be obtained, even after twice the minimal digitalizing dose. Contrariwise, as little as half the minimal dose may be effective in abolishing functional arrhythmias unassociated with heart disease.

The appearance of toxicity after a total dose of 0.6 mg. or less of acetylstrophanthidin is indicative of adequate or excessive digitalization. Indeed, as little as 25 μg. of acetylstrophanthidin per kilogram of body weight may produce toxicity in previously digitalized individuals.

Conclusions about adequate or excessive digitalization, on the basis of response to acetylstrophanthidin, are helpful but applicable only at the time of study because cardiac and extracardiac factors, which can change with time, are as, or at times more, important than the digitalis content of the body which may remain constant. Constant ECG surveillance is mandatory because ECG signs of toxicity are sudden in appearance and usually unaccompanied by systemic manifestations.

Characteristically, ventricular bigeminy is produced with constant coupling with or without multiform configuration. All types of conduction disturbances may be produced. Increased automaticity, manifested by ventricular premature beats or ectopic beats occurring in varying frequency with inconstant coupling or in salvos or a rapid ventricular response in atrial fibrillation, may herald ventricular fibrillation. The response to additional acetylstrophanthidin is unpredictable. If toxicity occurs, acetylstrophanthidin should be discontinued immediately for toxicity may disappear within minutes or may occasionally persist and even increase for variable periods, (up to 90 minutes after cessation of acetylstrophanthidin). Procaine amide which is usually effective in abolishing the ventricular ectopic arrhythmias may on rare occasions be followed by ventricular fibrillation. Systemic manifestations, such as nausea, vomiting and dizziness indicate incipient cardiac toxicity, if not already present.

**The Fluoroscopic Image Amplifier: Its Use for Cardiac Catheterization**

*Henry A. Zimmerman, Cleveland, O.*

In the past eight years a total of over 1,000 cardiac catheterizations have been carried out by the author. In the last 100 of these, the fluoroscopic image amplifier has been used.

Advantages to image amplification are as follows: (1) The catheter can be passed in a lighted room thus alleviating the patient's fear and apprehension of the dark. (2) It allows use of one's most acute vision, cone vision rather than rod vision, and does away with the long period of time it takes to become adapted to the dark. (3) It gives a three-dimensional effect to the catheter. (4) The catheter position can be seen at all times since contrast and definition are extremely good even over areas such as the spine, or as in a large heart, or a thick chested individual. (5) Irradiation to the patient and to the operator is cut by ⅓ to ½. (6) Pulmonary vascularity can be readily studied. The small area viewed is the only disadvantage to image amplification encountered. The field is five inches in diameter, but is readily accepted after adapting to it.

**Quinine and Quinidine Sulfate as Coronary Vasodilators**

*Burton L. Zohman, Alice E. Drumm and Henry I. Russek, New York, N. Y.*

As far back as 1898, it was shown that quinidine and quinine have a vasodilating action in laboratory animals. Because of the inapplicability of animal observations in man and the inaccuracy of clinical estimates of coronary efficiency that are based on the symptom of pain, we decided to record the ability of quinine and quinidine to modify the ECG response to standard exercise, (Master two-step test) in carefully selected cases. Only patients with coronary artery disease, who on repeated testing exhibited a relatively constant positive response to a given amount of exercise, were included. In addition, the control response could be favorably modified by the sublingual administration of therapeutic doses of nitroglycerine just before the test. By establishing this prerequisite, it was felt

that a basis for comparison could be obtained between the effect of the potent coronary vasodilator, nitroglycerine and that of quinine and quinidine sulfate. Two tests were performed in a single day. One and one-half and 3 hour studies were made on 1 day and 2 and 4 hour studies on the next. In a dose of 10 grains, quinine sulfate was found to exert a "good" to "very good" modifying influence for as long as 4 hours on the ECG response to standard exercise in 6 of 14 patients tested. There was no response in 8 patients. Similarly, in a dose of 6 grains, quinidine sulfate was found to effect a "good" to "very good" response in 7 of 13 patients tested and for as long as four hours.

It would seem from this study that quinine and quinidine sulfate have the ability to favorably modify the electrocardiographic response to exercise (Master two-step test) and that quinidine does so somewhat better than quinine. Both have a coronary vasodilator action and should be effective agents in the treatment of angina pectoris.

**Effects of Sympathomimetic Drugs on Ventricular Rhythmicity and Atrioventricular Conduction during Stokes-Adams Attacks**

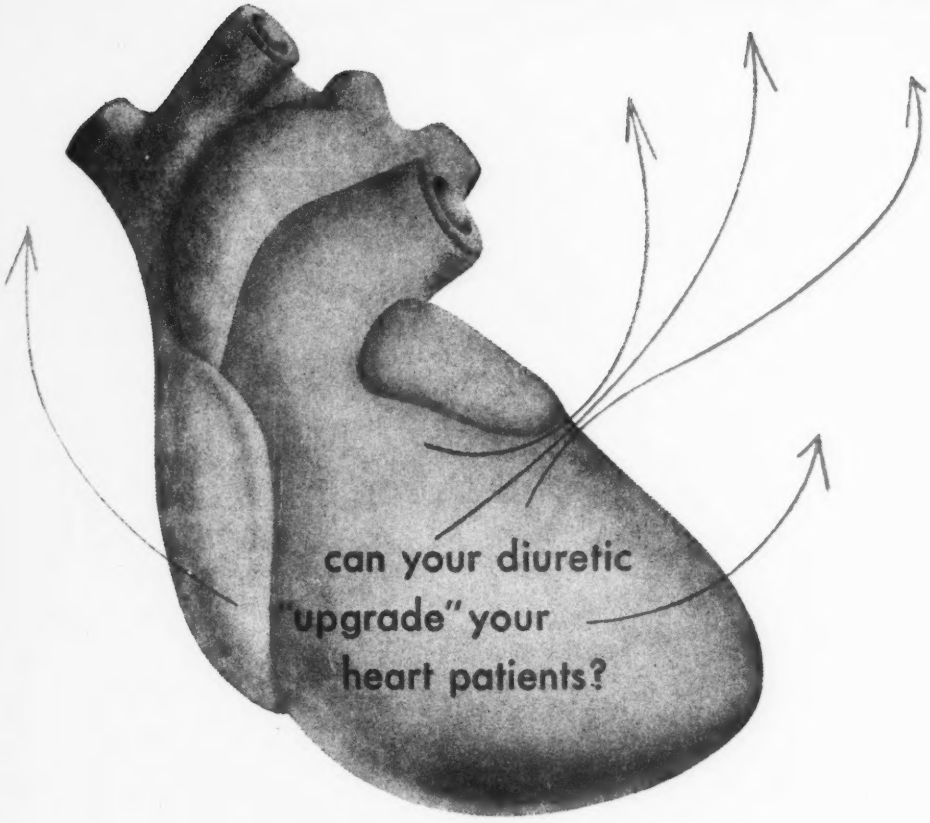
*Paul M. Zoll, Arthur J. Linenthal, William Gibson, Milton H. Paul and Leona R. Norman, Boston, Mass.*

Sympathomimetic amines are widely used as cardiac stimulants and vasopressor agents, but there is little precise information about their relative effects on cardiac rhythmicity, cardiac conductivity and blood pressure in man.

Unique opportunities to study and compare these actions quantitatively were presented by patients who were resuscitated from Stokes-Adams attacks and were kept alive by external electric stimulation of the heart for hours or days without spontaneous ventricular beats. In 6 of 23 such patients, sympathomimetic agents were given in carefully controlled intravenous infusions in order to arouse a spontaneous ventricular rhythm. During these therapeutic procedures, the relative magnitude, duration and dose-response relations of the various cardiac effects were determined.

Epinephrine, norepinephrine and isopropylnorepinephrine differed only quantitatively. Epinephrine appeared most effective for the excitation, acceleration and maintenance of an idioventricular pacemaker; these responses often occurred promptly with doses (4 to 10 μg. per minute) which did not excite ectopic ventricular activity and did not affect the blood pressure significantly, even in patients with hypertension. The small doses of norepinephrine, required to elevate the blood pressure, sometimes excited ectopic ventricular activity which terminated at once, when the drug was stopped. Isopropylnorepinephrine sometimes excited multifocal ventricular activity in the same dose, required to arouse an idioventricular pacemaker; it had no vasopressor action. Careful comparison of the effects of these and other sympathomimetic amines delineated their beneficial and untoward actions and indicated the agent of choice for each of a variety of specific therapeutic purposes.

All these agents often restored some degree of atrioventricular conduction. This action indicates a functional basis, in addition to the known structural changes, for atrioventricular block. The actions of these drugs, on cardiac rhythmicity and atrioventricular conduction, support a pharmacologic approach to the treatment of heart block itself, as well as for the Stokes-Adams attacks.

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